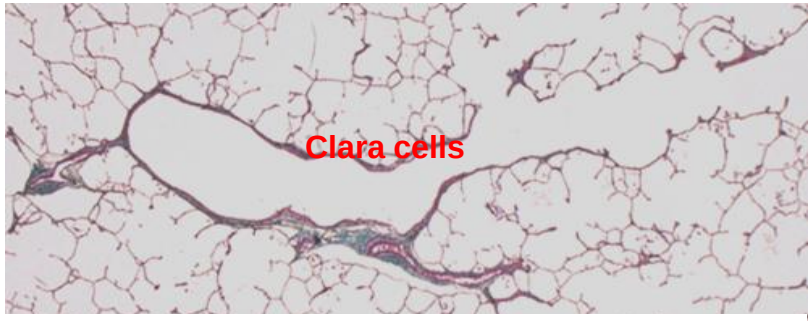
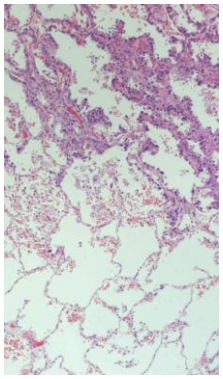
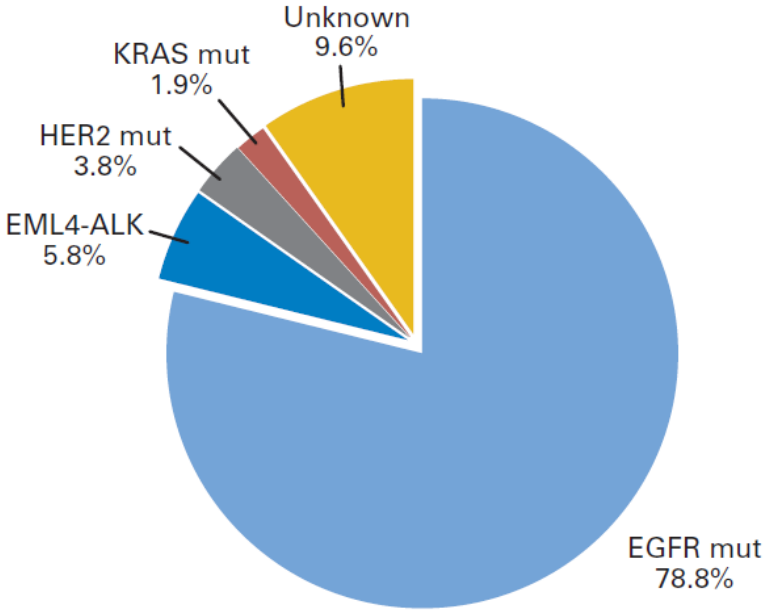
肺腺癌分子標的薬:その後の展開-調べれば肺腺癌はdriver変異ばかり-

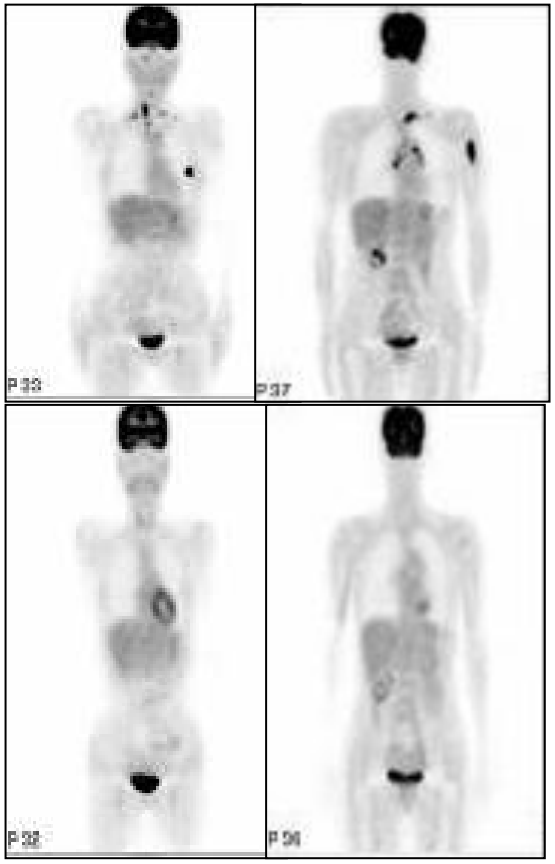
肺腺癌分子標的薬：その後の展開

～調べれば肺腺癌はdriver変異ばかり～









東北大学大学院医学系研究科
呼吸器病態学分野
東北大学病院呼吸器内科
貫和　敏博

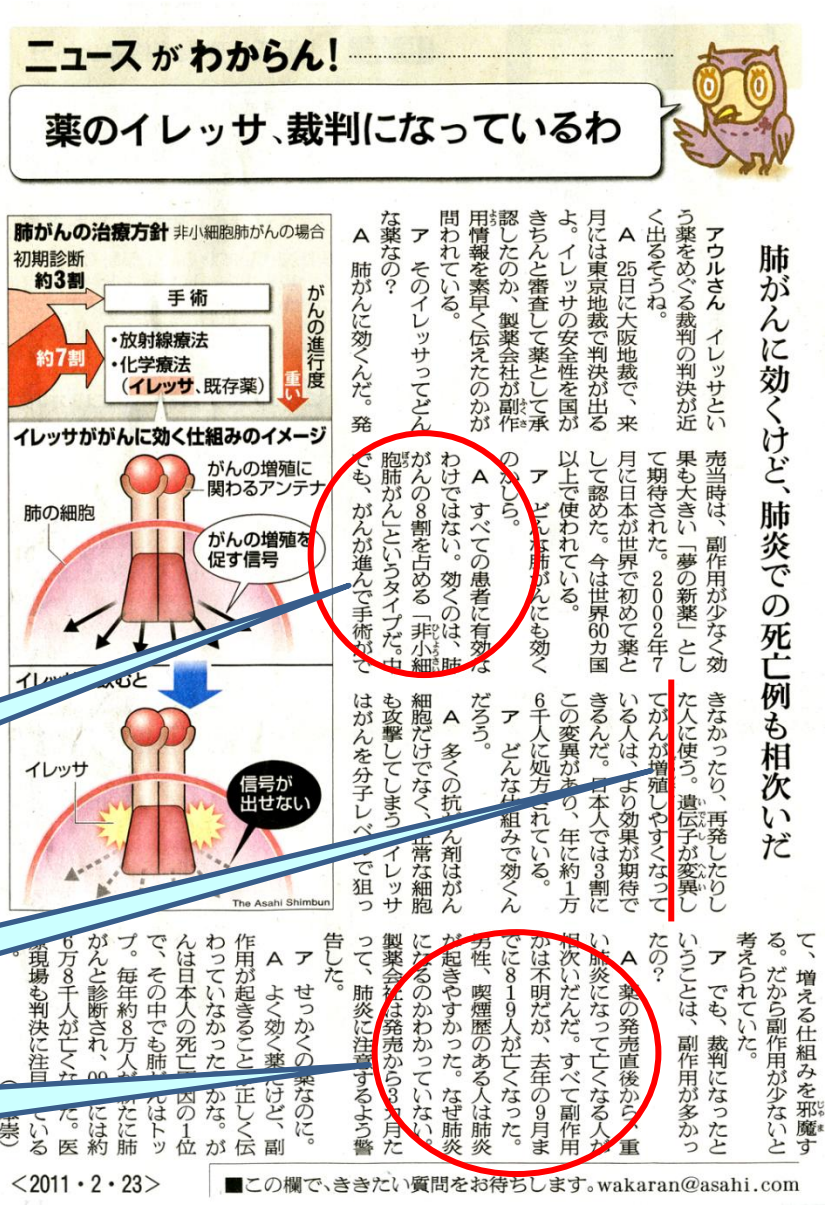
個別化医療への誤解

NHK若手O記者の言葉

「先生、ある人だけにしか効かない薬というのは、おかしい．薬は患者誰にでも効くべきだと思います．」

皆さんは、どうお考えになりますか？

なぜ、ある人は効いて、他の人には効かないのか？個別化医療はなぜ成立するのか？



ニュースがわからん!

薬のイレッサ、裁判になっているわ

肺がんに効くけど、肺炎での死亡例も相次いだ

アウルさん　イレッサという薬をめぐる裁判の判決が近く出るそうね。

A　25日に大阪地裁で、来月には東京地裁で判決が出るよ。イレッサの安全性を国がきちんと審査して薬として承認したのか、製薬会社が副作用情報を素早く伝えたのかが問われている。

ア　そのイレッサってどんな薬なの？

A　肺がんに効くんだ。発売当時は、副作用が少なく効果も大きい「夢の新薬」として期待された。2002年7月に日本が世界で初めて薬として認めた。今は世界60カ国以上で使われている。

ア　どんな肺がんにも効くのかしら。

A　すべての患者に有効なわけではない。効くのは、肺がんの8割を占める「非小細胞肺がん」というタイプだ。中でも、がんが進んで手術ができなかったり、再発したりした人に使う。遺伝子が変異してがんが増殖しやすくなっている人は、より効果が期待できるんだ。日本人では3割にこの変異があり、年に約1万6千人に処方されている。

ア　どんな仕組みで効くんだろう。

A　多くの抗がん剤はがん細胞だけでなく、正常な細胞も攻撃してしまう。イレッサはがんを分子レベルで狙って、増える仕組みを邪魔する。だから副作用が少ないと考えられていた。

ア　でも、裁判になったということは、副作用が多かったの？

A　薬の発売直後から、重い肺炎になって亡くなる人が相次いだんだ。すべて副作用かは不明だが、去年の9月までに819人が亡くなった。男性、喫煙歴のある人は肺炎が起きやすかった。なぜ肺炎になるのかわかっていない。製薬会社は発売から3カ月たって、肺炎に注意するよう警告した。

ア　せっかくの薬なのに。

A　よく効く薬だけど、副作用が起きることも正しく伝わっていなかったかな。がんは日本人の死亡原因の1位で、その中でも肺がんはトップ。毎年約8万人が新たに肺がんと診断され、09年には約6万8千人が亡くなった。医薬現場も判決に注目している。（小宗）

<2011・2・23>

■この欄で、ききたい質問をお待ちします。wakaran@asahi.com

肺がんの治療方針　非小細胞肺がんの場合

初期診断　約3割　手術

約7割　・放射線療法　・化学療法（イレッサ、既存薬）

がんの進行度　重い

イレッサがんに効く仕組みのイメージ

がんの増殖に関わるアンテナ

肺の細胞

がんの増殖を促す信号

イレッサ

信号が出せない

The Asahi Shimbun

NSCLCと adenocarcinoma

増殖抑制か 抗細胞死抑制か

では具体的に 施策として何を？

個別化医療のKey word：Driver変異とは？

Vol 446|8 March 2007 nature

NEWS & VIEWS

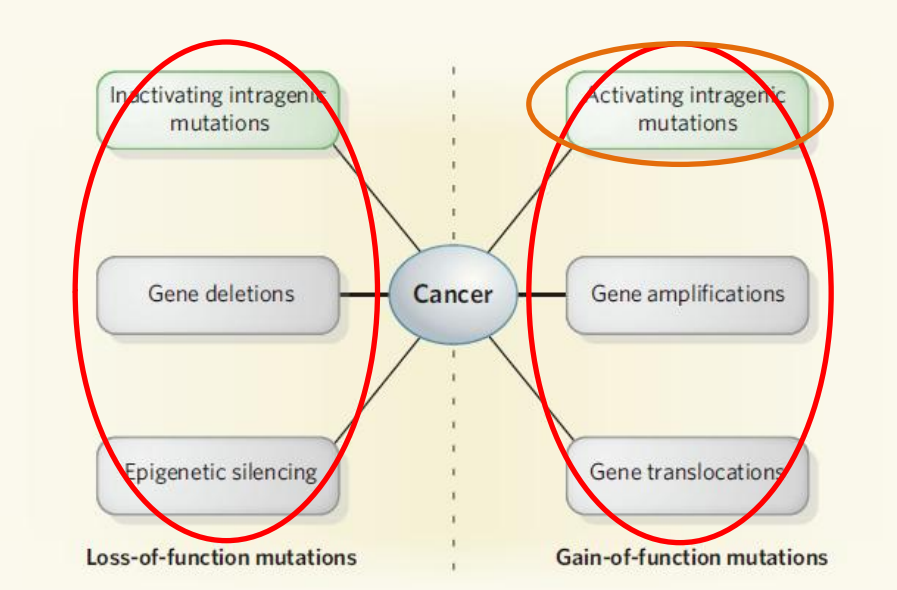
CANCER

Drivers and passengers

Daniel A. Haber and Jeff Settleman

Studies that have provided the first unbiased, large-scale analyses of DNA mutations across an array of cancers also have lessons for the proposal to annotate the entire cancer genome.

By the time a cancer is diagnosed, it comprises billions of cells carrying the DNA abnormalities that initiated malignant proliferation and many additional genetic lesions acquired along the way. Some of these secondary mutations emerge owing to selective pressure during tumorigenesis (drivers); others may be incidental (passengers), resulting from mutational exposures, genome instability or simply the large number of cell doublings that leads from a single transformed cell to a clinically detectable cancer. To distinguish driver from passenger mutations, Greenman et al. used a statistical model comparing the observed-to-expected ratio of synonymous (no amino-acid change) mutations with that of non-synonymous (altered amino acid) mutations. An increased proportion of non-synonymous mutations implies selection pressure during tumorigenesis.



Driver（運転士）変異：癌化への選択圧による変異（増殖、不死化を帰結する：治療標的になりうる）

Passenger（乗客）変異：偶然、易変異性で発生（変異の存在は癌生存に重要ではない）

運転助手・機関士的染色体変化は？

Driver変異
- 組織癌特異性、組織癌集積性があるのでないか？
- さらに人種間頻度も異なるとは？

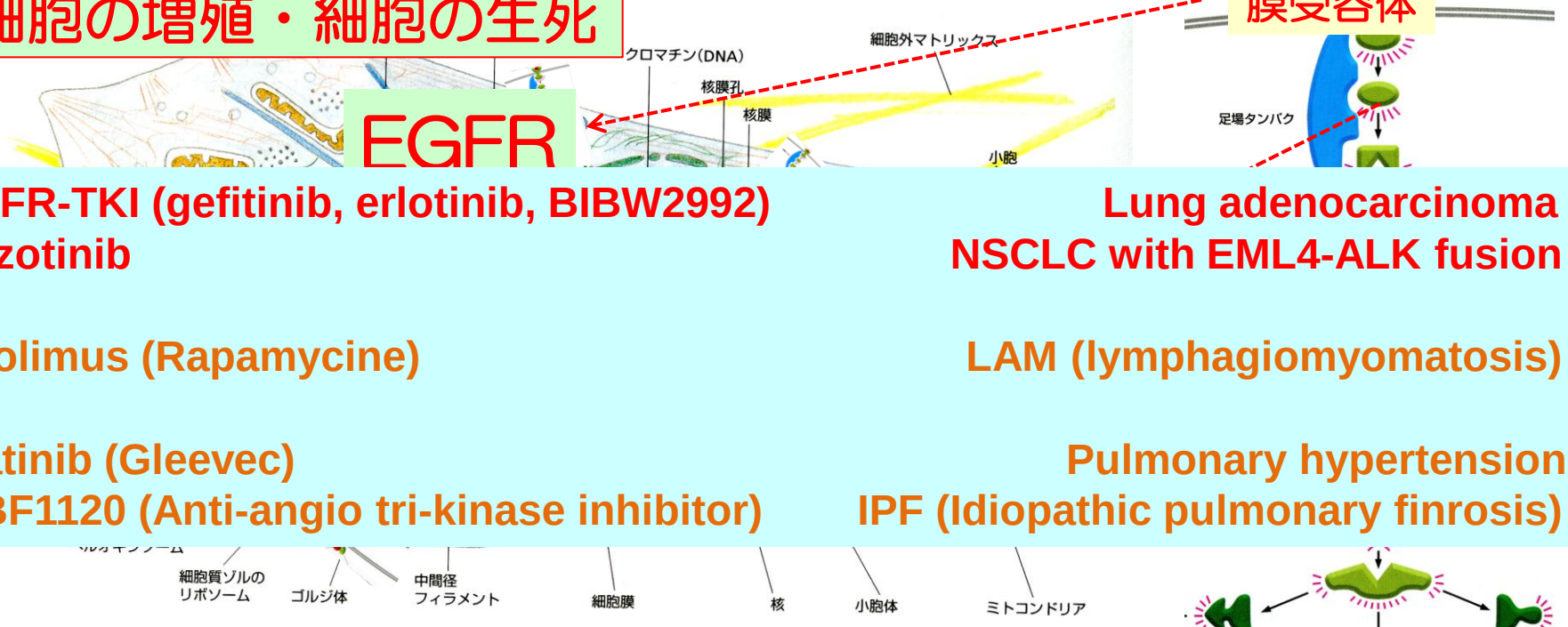
がん治療からすれば個別化の原点

肺がん細胞のDriver変異とシグナル

細胞の増殖・細胞の生死

EGFR

膜受容体



EGFR-TKI (gefitinib, erlotinib, BIBW2992) — **Lung adenocarcinoma**

Crizotinib — **NSCLC with EML4-ALK fusion**

Sirolimus (Rapamycine) — **LAM (lymphagiomyomatosis)**

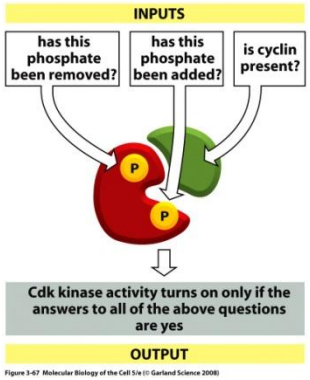
Imatinib (Gleevec) — **Pulmonary hypertension**

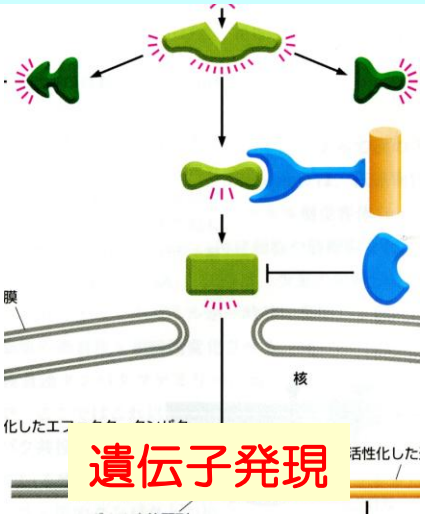
BIBF1120 (Anti-angio tri-kinase inhibitor) — **IPF (Idiopathic pulmonary finrosis)**

市民理解の少ないシグナル伝達
- 蛋白・蛋白相互作用
- リン酸化と３次元構造
- 蛋白質はmicrochip

↓

分子標的は情報処理の中枢を潰す

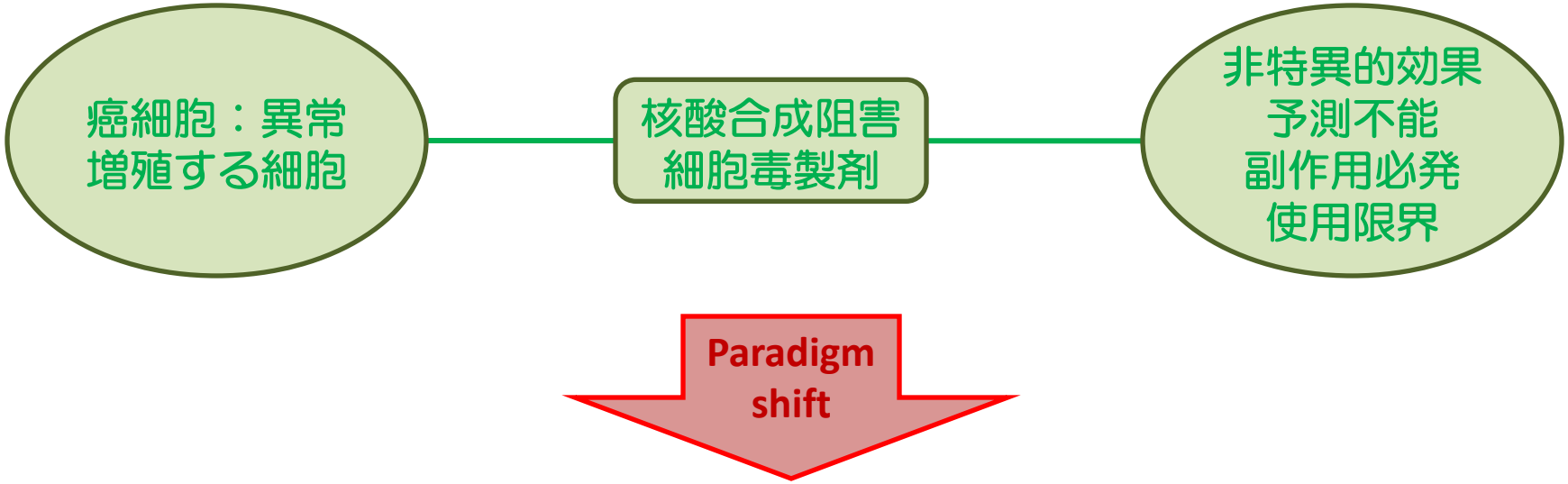




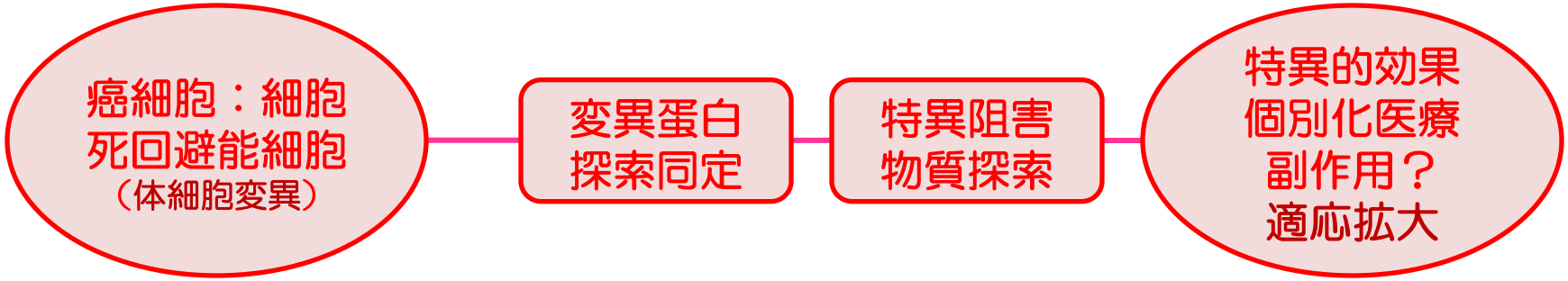
遺伝子発現

分子標的薬：何がParadigm Shiftか？

●従来の癌治療パラダイム：細胞を殺す=患者を苦しめる副作用



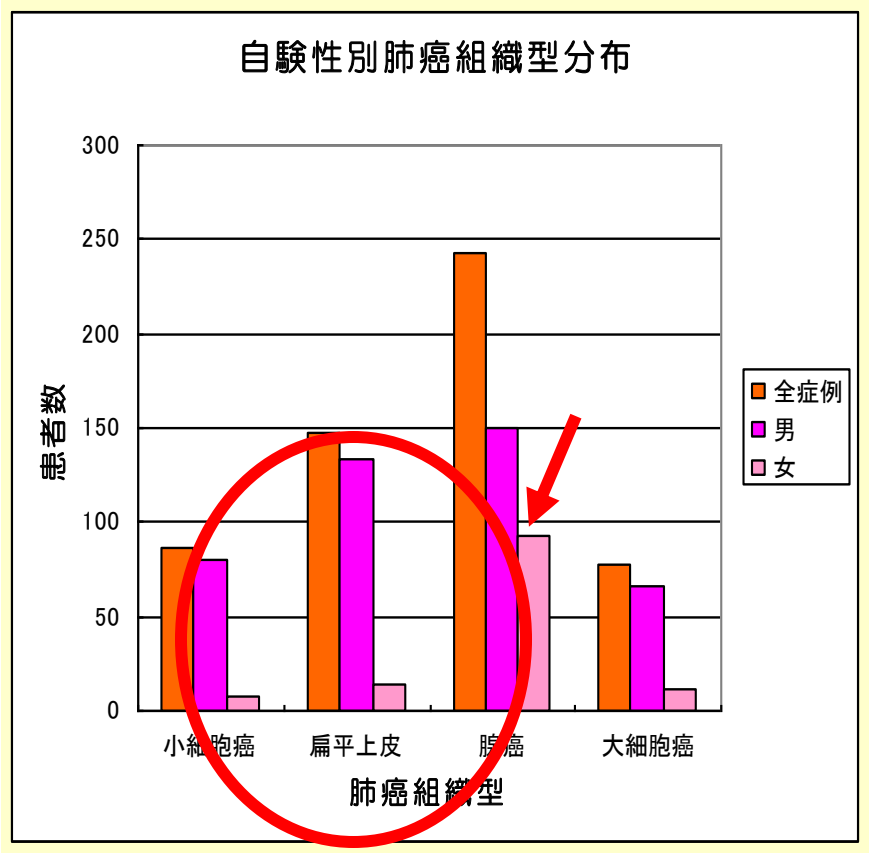
●新規の癌治療パラダイム：抗細胞死機構（driver変異）を阻害する=細胞死を誘発



しかも！体細胞変異は組織特異性・人種差異が見られる！

タバコが分ける肺がん分類：男性優位の肺がんとは？

組織系	(%)	部位	原因	倍増時間	抗がん剤感受性
扁平上皮がん	30	近位	タバコ	約100日	中等度
小細胞がん	15	近位	タバコ	約80日	高感受性
腺がん	50	末梢	タバコを吸わない人も	約200日	抵抗性



・その他大細胞がんもある
・小細胞肺がんをSCLC、それ以外の組織型を非小細胞肺がんNSCLCと略する

男の肺がんに注目
・小細胞肺がん
・扁平上皮がん
↓
タバコが原因の肺がん

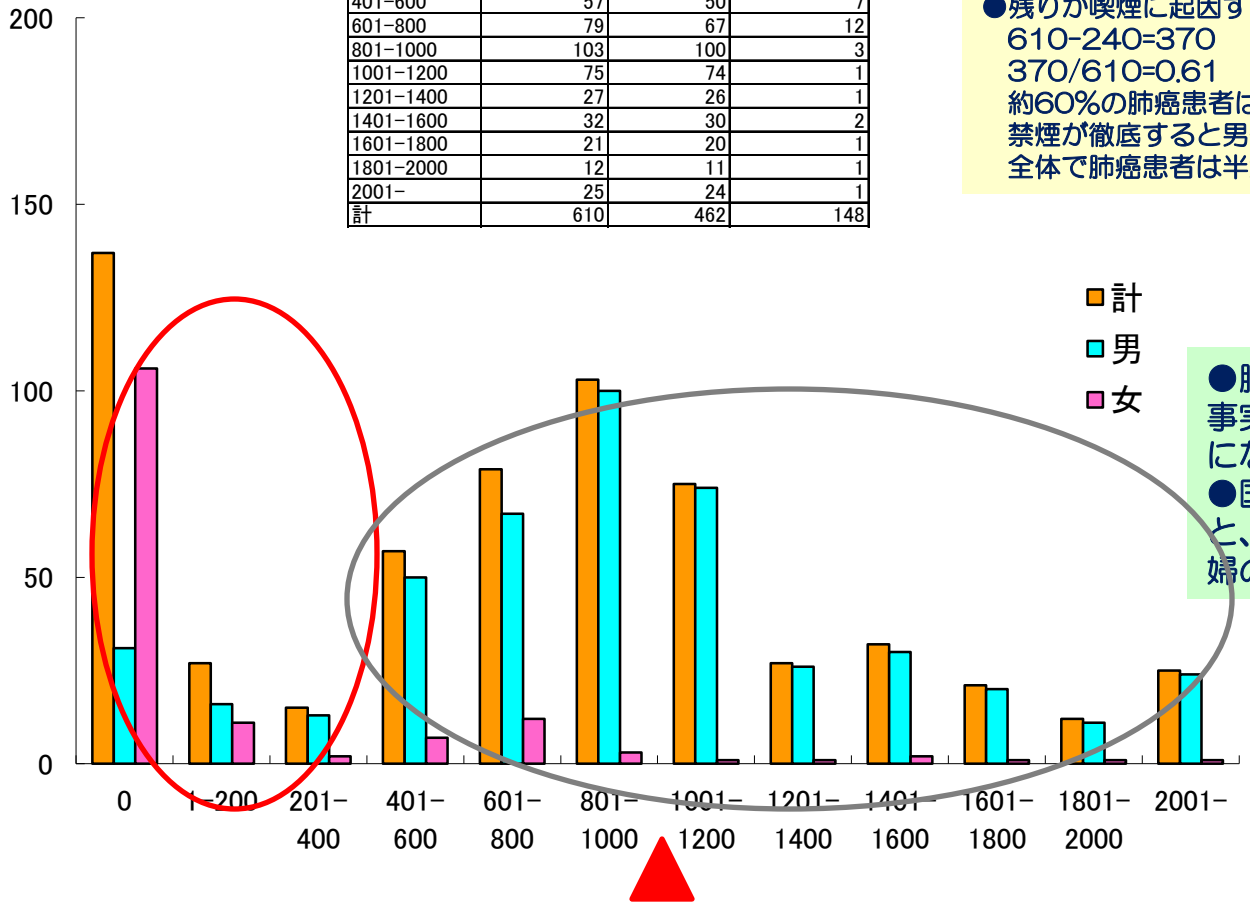
・組織型の分布は腺癌が増加する傾向がある
・女性（非喫煙者）の肺癌はほとんどが肺腺癌（７４％）　である（矢印↓参照）

非喫煙者肺がんに注目
・肺腺癌
↓
個別化医療の突破口

喫煙指数（本数x年数）の分布：財務省の弱腰が変化？

東北大学病院呼吸器内科肺癌患者喫煙指数分布
（2003.11 - 2008.10）

喫煙指数	計	男	女
0	137	31	106
1-200	27	16	11
201-400	15	13	2
401-600	57	50	7
601-800	79	67	12
801-1000	103	100	3
1001-1200	75	74	1
1201-1400	27	26	1
1401-1600	32	30	2
1601-1800	21	20	1
1801-2000	12	11	1
2001-	25	24	1
計	610	462	148



●男女肺癌患者では喫煙指数に大きな差がある.
●喫煙指数には二峰性が見られる.
●喫煙指数0-400を喫煙非関連と仮定すると、
このグループに女子は120名
性差がないとすると、男子も非喫煙者肺癌が120名.
●残りが喫煙に起因する肺発癌と考えると、
610-240=370
370/610=0.61
約60%の肺癌患者は喫煙関連.
禁煙が徹底すると男性で60%患者減少.
全体で肺癌患者は半減する.

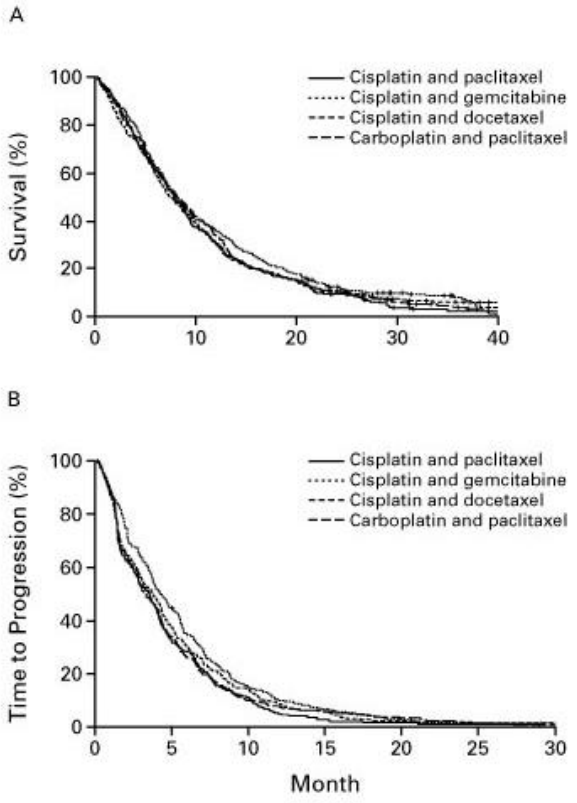
●肺癌がニコチン依存から発生する事実が明らかになりつつある（公知になる）.
●国ははっきり喫煙規制をしないと、本人より学資を失った子弟や夫婦の生活費等の訴訟が起こりうる.

喫煙指数が1000=36.5万本のタバコ・・・これは動物実験だ！ニコチン弱者が被験者

Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer

Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH; The Eastern Cooperative Oncology Group.
University of Wisconsin Hospital and Clinics, Madison, USA.

BACKGROUND: We conducted a randomized study to determine whether any of three chemotherapy regimens was superior to cisplatin and paclitaxel in patients with advanced non-small-cell lung cancer. METHODS: A total of 1207 patients with advanced non-small-cell lung cancer were randomly assigned to a reference regimen of cisplatin and paclitaxel or to one of three experimental regimens: cisplatin and gemcitabine, cisplatin and docetaxel, or carboplatin and paclitaxel.RESULTS: The response rate for all 1155 eligible patients was 19 percent, with a median survival of 7.9 months (95 percent confidence interval, 7.3 to 8.5), a 1-year survival rate of 33 percent (95 percent confidence interval, 30 to 36 percent), and a 2-year survival rate of 11 percent (95 percent confidence interval, 8 to 12 percent). The response rate and survival did not differ significantly between patients assigned to receive cisplatin and paclitaxel and those assigned to receive any of the three experimental regimens. Treatment with cisplatin and gemcitabine was associated with a significantly longer time to the progression of disease than was treatment with cisplatin and paclitaxel but was more likely to cause grade 3, 4, or 5 renal toxicity (in 9 percent of patients, vs. 3 percent of those treated with cisplatin plus paclitaxel). Patients with a performance status of 2 had a significantly lower rate of survival than did those with a performance status of 0 or 1. CONCLUSIONS: None of four chemotherapy regimens offered a significant advantage over the others in the treatment of advanced non-small-cell lung cancer.



対象：IIIB, IV期 NSCLC
1．CDDP + TXL
2．CDDP + GEM
3．CDDP + TXT
4．CBDCA + TXL
各群　300名

結果：
MST(50%生存期間）は８ヶ月でほぼ同じ.
奏効率：20%前後
副作用には差があり

NEJM, 346: 92-8, 2002.

この時のeditorialのタイトルは「Lung Cancer — Time to Move on from Chemotherapy」であった。

●未知の領域ー肺癌遺伝子治療への挑戦：なぜ遺伝子治療を考えたか？

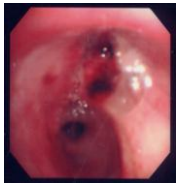
●Adenovirusのシステムをいかに移植、定着させるか

●米国への留学・経験
国内研究施設との連携

●優秀な人材に恵まれたから可能であった

気管支鏡による遺伝子注入

注入前



注入後

●Adenovirusによるp53 遺伝子導入臨床試験

●現在のTRを10年前に実践していた
大学間連携臨床試験
2例の臨床試験実施

しかし実効性のないことを自己批判

VOLUME 24 · NUMBER 11 · APRIL 10 2006

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Multicenter Phase I Study of Repeated Intratumoral Delivery of Adenoviral *p53* in Patients With Advanced Non–Small-Cell Lung Cancer

Toshiyoshi Fujiwara, Noriaki Tanaka, Susumu Kanazawa, Shoichiro Ohtani, Yasuo Saijo, Toshihiro Nukiwa, Kunihiko Yoshimura, Tetsuo Sato, Yoshikatsu Eto, Sunil Chada, Haruhiko Nakamura, and Haruhumi Kato

From the Center for Gene and Cell Therapy, Okayama University Hospital; Departments of Surgery and Radiology, Okayama University Graduate School of Medicine and Dentistry; Okayama; Department of Molecular Medicine, Tohoku University Graduate School of Medicine; Department of Respiratory Oncology and Molecular Medicine, Institute of Developing, Aging, and Cancer, Tohoku University, Sendai; Department of Gene Therapy, Institute of DNA Medicine, Department of Respiratory Medicine, Jikei University School of Medicine; Department of Surgery, Tokyo Medical University, Toyko, Japan; and Introgen Therapeutics Inc, Houston, TX.

Submitted August 1, 2005; accepted December 8, 2005.

Supported by grants from the Ministry of Education, Science, and Culture, Japan; and by grants from the Ministry of Health, Labour, and Welfare, Japan.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/06/2411-1689/$20.00

DOI: 10.1200/JCO.2005.03.4116

ABSTRACT

Purpose
To determine the feasibility, safety, humoral immune response, and biologic activity of multiple intratumoral injections of Ad5CMV-p53, and to characterize the pharmacokinetics of Ad5CMV-p53 in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Fifteen patients with histologically confirmed NSCLC and *p53* mutations were enrolled onto this phase I trial. Nine patients received escalating dose levels of Ad5CMV-p53 (1×10^9 to 1×10^{11} plaque-forming units) as monotherapy once every 4 weeks. Six patients were treated on a 28-day schedule with Ad5CMV-p53 in combination with intravenous administration of cisplatin (80 mg/m^2). Patients were monitored for toxicity, vector distribution, antibody formation, and tumor response.

Results
Fifteen patients received a total of 63 intratumoral injections of Ad5CMV-p53 without dose-limiting toxicity. The most common treatment-related toxicity was a transient fever. Specific *p53* transgene expression was detected using reverse-transcriptase polymerase chain reaction in biopsied tumor tissues throughout the period of treatment despite of the presence of neutralizing antiadenovirus antibody. Distribution studies revealed that the vector was detected in the gargle and plasma, but rarely in the urine. Thirteen of 15 patients were assessable for efficacy; one patient had a partial response (squamous cell carcinoma at the carina), 10 patients had stable disease, with three lasting at least 9 months, and two patients had progressive disease.

Conclusion
Multiple courses of intratumoral Ad5CMV-p53 injection alone or in combination with intravenous administration of cisplatin were feasible and well tolerated in advanced NSCLC patients, and appeared to provide clinical benefit.

J Clin Oncol 24:1689-1699. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the most common cause of cancer related deaths in both men and women worldwide.[1] In 2001, 39,880 males and 15,122 females died of lung cancer in Japan, which ranked first among males and third among females in the number of cancer deaths.[2] Recent advances in molecular biology have fostered remarkable insights into the molecular basis of lung cancer,[3] and suggest that restoration of the function of critical gene products could halt or reverse cancer pathogenesis, thus having a therapeutic effect in cancer.

p53 is the most extensively studied tumor suppressor gene, and its mutation has been reported to be one of the most common genetic changes found in malignant tumors.[4] *p53* gene mutation is reported to occur in 40% to 50% of non–small-cell lung cancer (NSCLC),[5] and aberrant *p53* expression correlates with an adverse prognosis in lung cancers.[6,7] The *p53* gene product is involved in multiple pivotal cellular processes as a potent transcriptional regulator, and one of its most important roles is in the regulation of apoptosis.[8] We previously reported that the overexpression of the wild-type *p53* (wt-*p53*) gene by recombinant, replication-deficient viral vector, Ad5CMV-p53 (ADVEXIN; Introgen Therapeutics Inc, Houston, TX), triggered apoptosis in a variety of human cancer cells independent of their *p53* status.[9-15] ADVEXIN in combination with chemotherapeutic drugs, such as cisplatin, showed a profound antitumor effect in

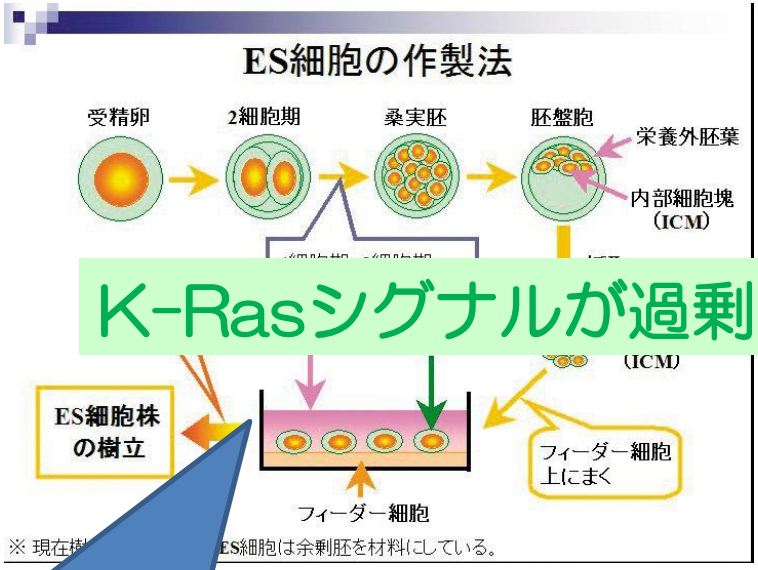
●遺伝子治療はなぜ実効医学になれなかったか

●不十分なTRレベルでのアデノウイルス作成
過剰投与による患者死亡
COI上も問題が指摘された

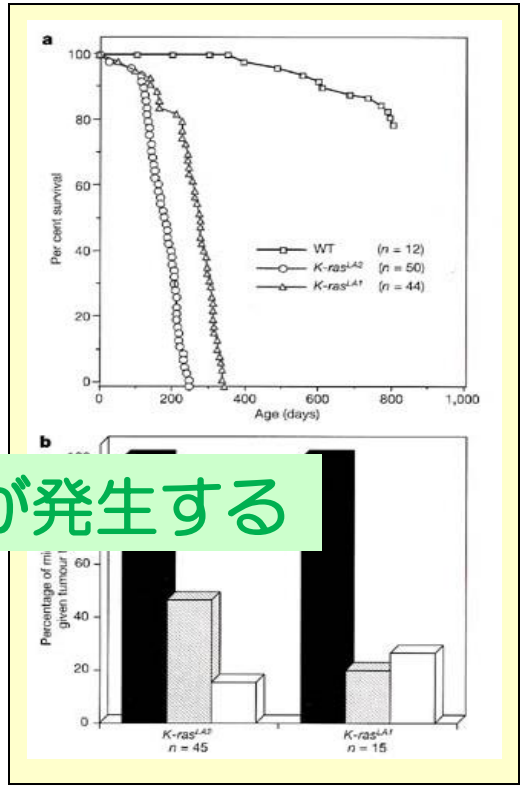
●レトロウイルスベクターによるlynphoma発症
先天性免疫不全症も進まなくなった

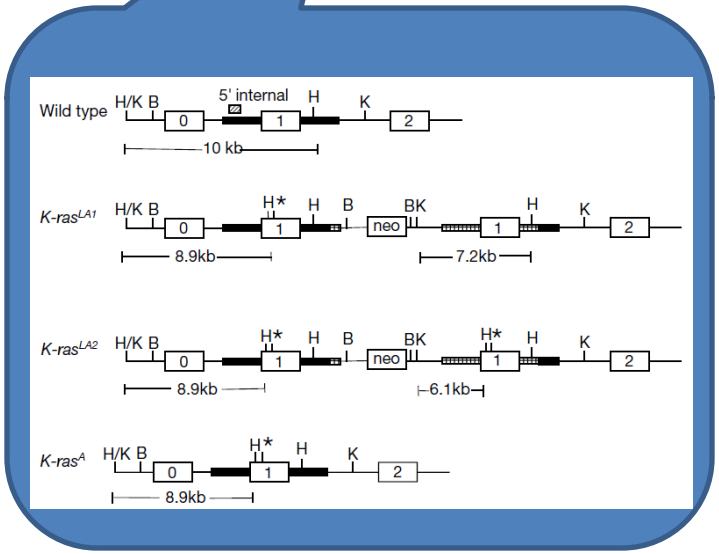
しかし、医局員のBasic molecular biologyへの素養が次の展開に繋がった！

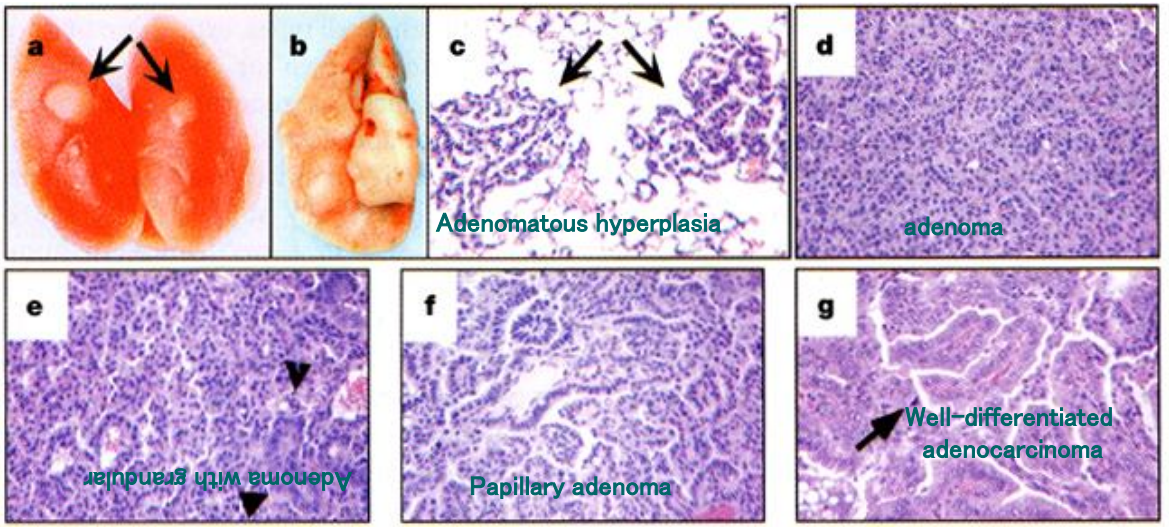
Nature 2001 Apr 26;410(6832):1111-6
Somatic activation of the K-ras oncogene causes early onset lung cancer in mice.
Johnson L, Mercer K, Greenbaum D, Bronson RT, Crowley D, Tuveson DA, Jacks T.



K-Rasシグナルが過剰に流れると肺癌が発生する



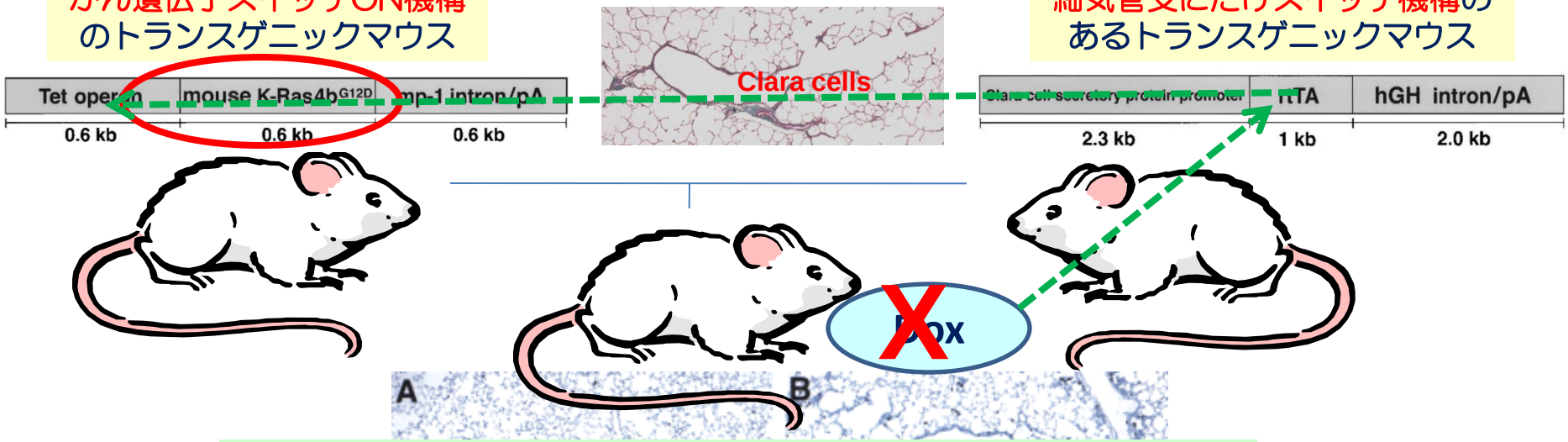




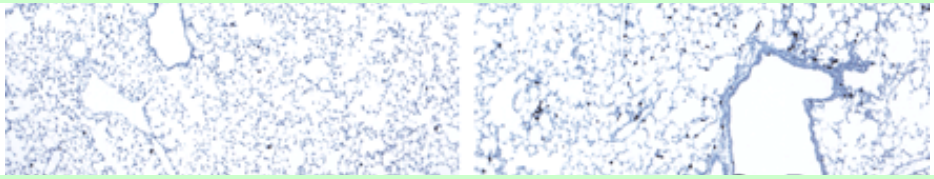
Driver変異であるk-Ras：スイッチ・オンで肺がんになるマウス

がん遺伝子スイッチON機構
のトランスゲニックマウス

細気管支にだけスイッチ機構の
あるトランスゲニックマウス

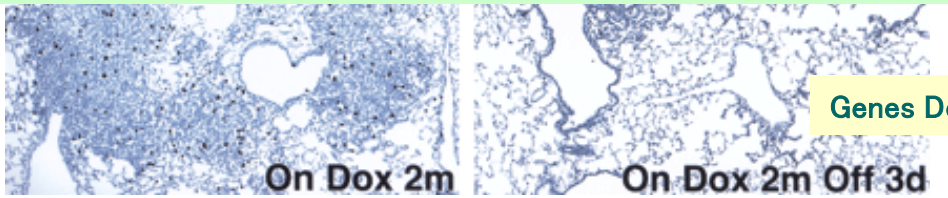


細気管支だけでがん遺伝子が働くと肺がんが発生する



がん遺伝子を働かなくすると短時間で肺がんは消える
(シグナルが流れないと)

分子標的薬の治療効果の説明？

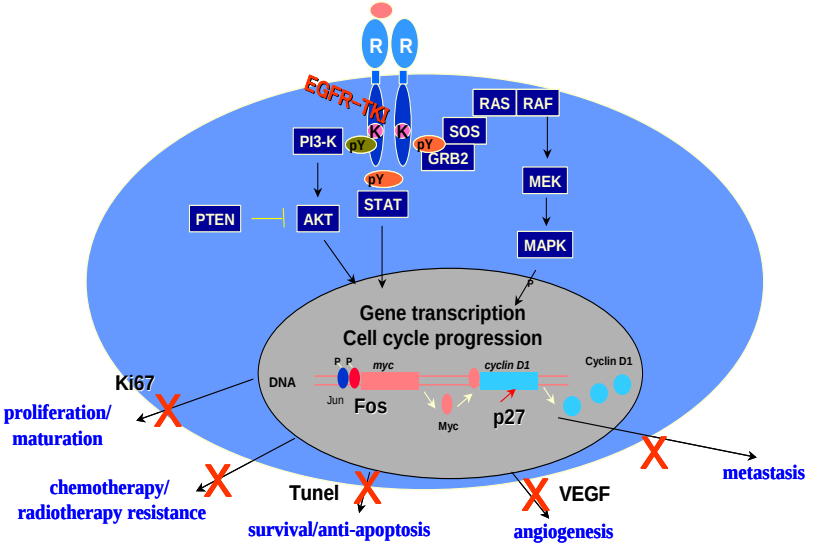


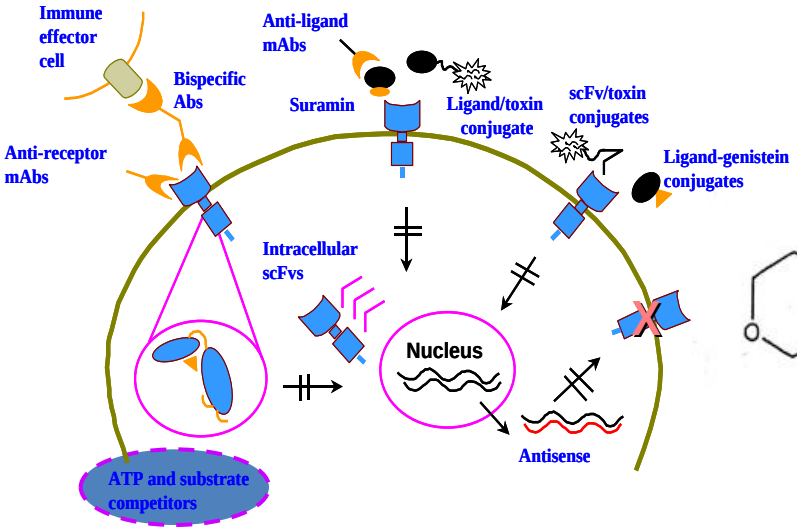
Genes Dev 2001, 15, :3249-62

癌細胞標的EGF受容体：シグナルの多様な阻害方法と創薬

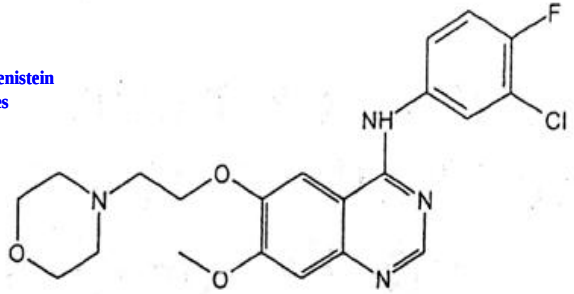
EGF受容体
高発現の見られる癌腫
- 非小細胞肺癌（40-80%）
- 前立腺癌（40-80%）
- 胃癌（33-74%）
- 乳癌（14-91%）
- 大腸癌（25-77%）
- 膵癌（30-50%）
- 卵巣癌（35-70%）

EGF受容体高発現と癌の性質
- 浸潤
- 転移
- 抗癌剤耐性
- 悪液質





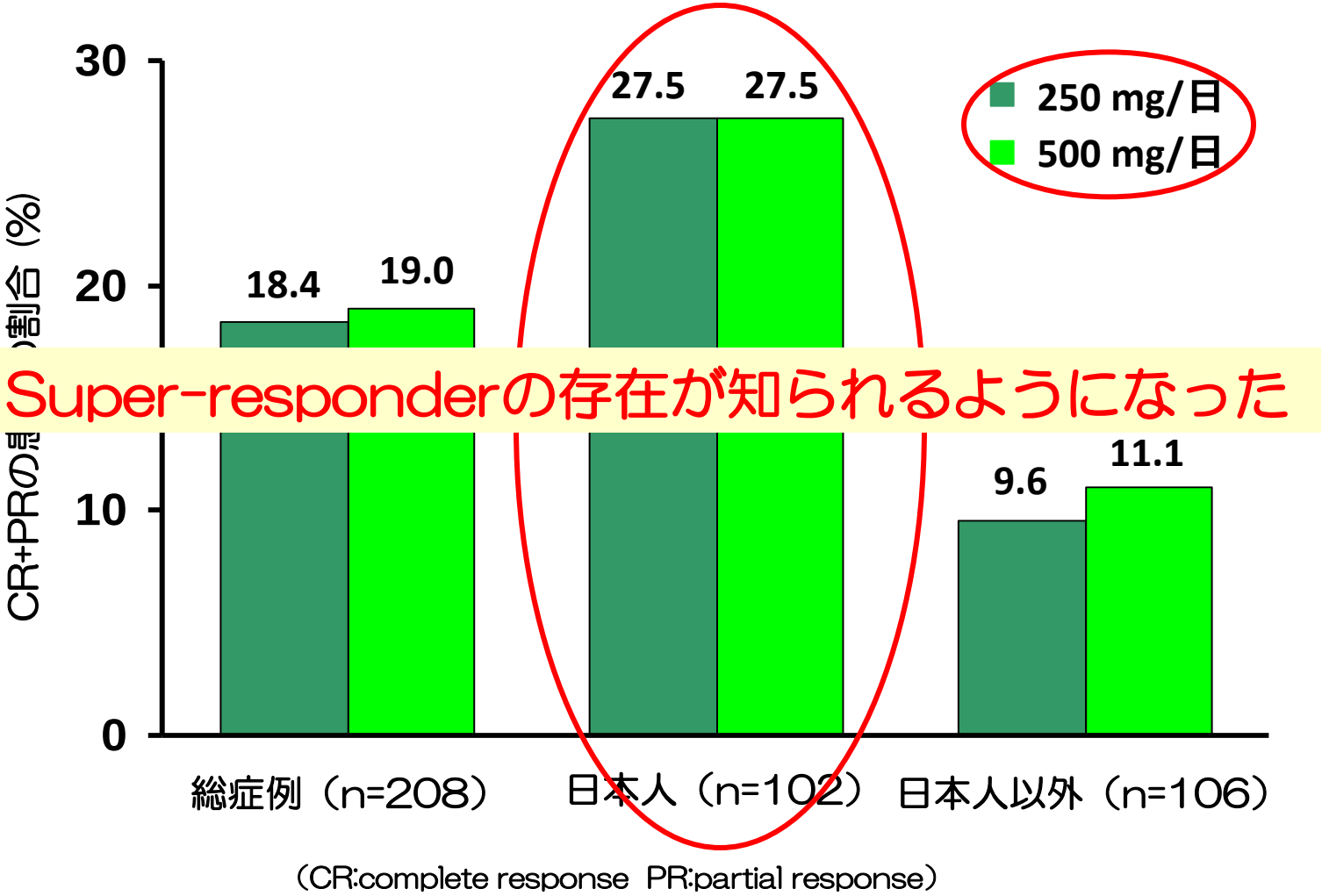
EGFR inhibition by ZD1839



- Chemical class: quinazoline
- ***Orally bioavailable***
- Selective inhibitor of EGFR tyrosine kinase
  - EGFR IC_{50} = 0.023-0.079 μM
  - erbB2 IC_{50} = 1.2-3.7 μM
- Competitive inhibitor of ATP
- Inhibits ligand-induced cell growth
  - IC_{50} = 0.080 μM

AstraZeneca ONCOLOGY

臨床試験 IDEAL 1における奏功率：驚きと疑問



（CR:complete response PR:partial response）

Fukuoka M, et al: J Clin Oncol, 21, 2237-46, 2003

Published at www.nejm.org April 29, 2004

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., …and Daniel A. Haber, M.D., Ph.D.

Catalytic kinase domain somatic mutation
Lung adenoicarcinomaで特異な変異やアミノ酸欠落が存在する（Lynch TJ, N Engl J Med, 350, 2004; Paez JG, Science, 304, 2004）
患者で共通した変異やアミノ酸欠落を２施設で報告

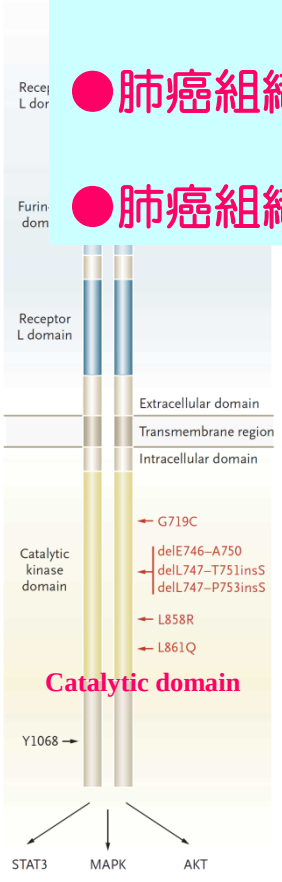
Table 2. Somatic Mutations in the Tyrosine Kinase Domain of EGFR in Patients with Non–Small-Cell Lung Cancer.

Patient	Mutation	Effect of Mutation
Patients with a response to gefitinib		
Patient 1	Deletion of 15 nucleotides (2235–2249)	In-frame deletion (746–750)
Patient 2	Deletion of 12 nucleotides (2240–2251)	In-frame deletion (747–751) and insertion of a serine residue
Patient 3	Deletion of 18 nucleotides (2240–2257)	In-frame deletion (747–753) and insertion of a serine residue
Patient 4	Deletion of 18 nucleotides (2240–2257)	In-frame deletion (747–753) and insertion of a serine residue
Patient 5	Substitution of G for T at nucleotide 2573	Amino acid substitution (L858R)
Patient 6	Substitution of G for T at nucleotide 2573	Amino acid substitution (L858R)
Patient 7	Substitution of A for T at nucleotide 2582	Amino acid substitution (L861Q)

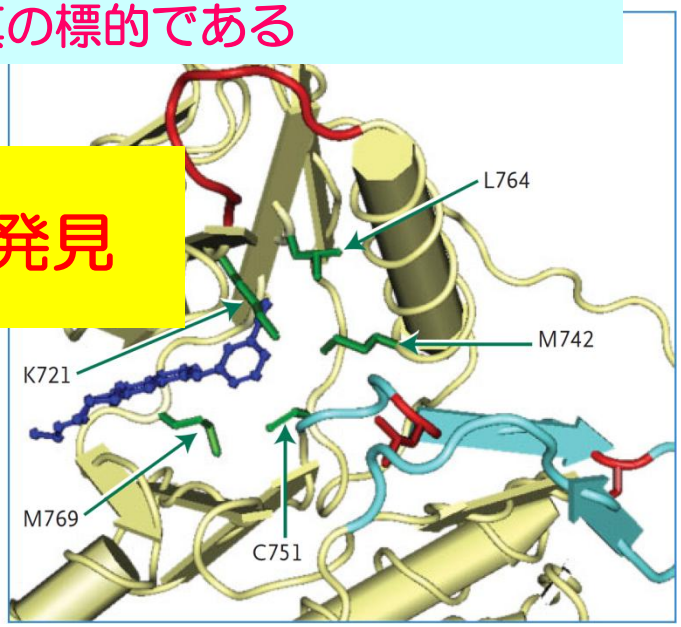
●肺癌組織EGF受容体のリン酸化酵素部分に特異な変異が集積する

●肺癌組織EGF受容体リン酸化酵素の変異はactivating mutataionである

●肺癌組織EGF受容体リン酸化酵素の変異こそ真の標的である



肺腺癌Driver変異の発見

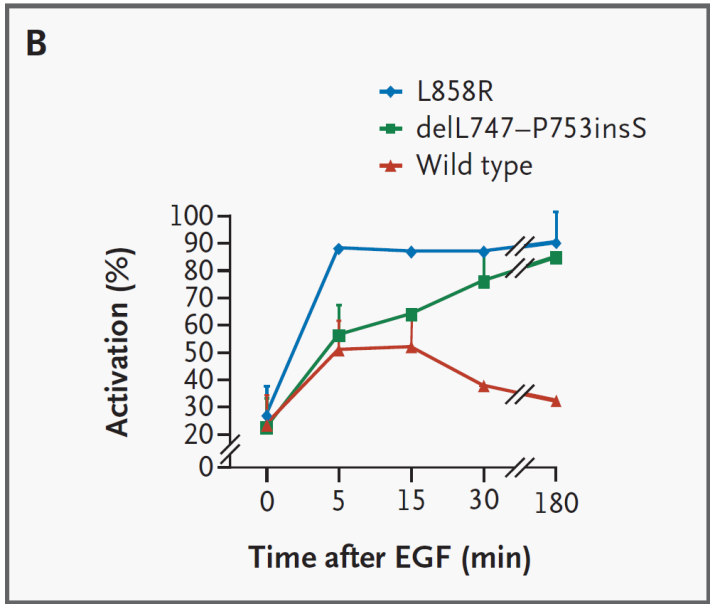


Notice: To coincide with the online release of similar findings by Science, this article was published at www.nejm.org on April 29, 2004. It will appear in the May 20 issue of the Journal

分子標的薬のtargetは
体細胞変異蛋白だ！
（driver変異蛋白）

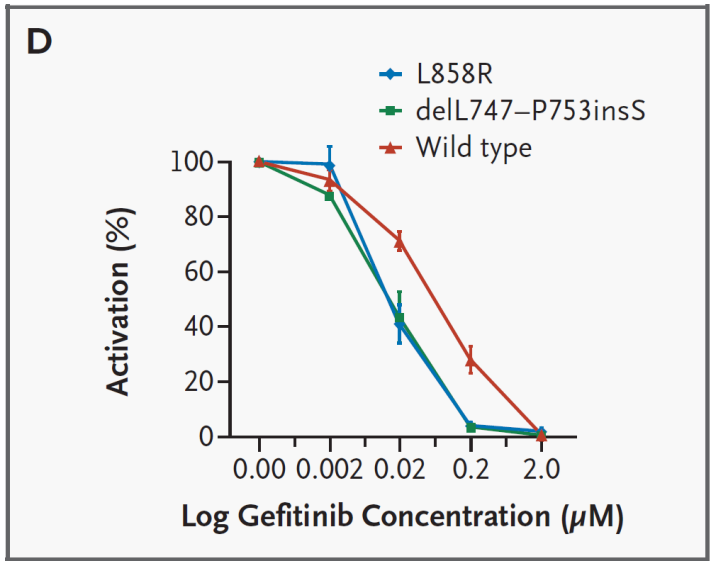
まさか！

肺腺癌組織のEGFR変異はactivating mutationである



臨床検体に見いだされた変異のある細胞はEGF受容体の自己リン酸化が持続する

活性型変異である
Driver変異である



臨床検体に見いだされた変異のある細胞ではgefitinibの阻害作用が10倍強い

野生型より親和性
個別化医療に応用

NEJM 2004, 350 :2129–39

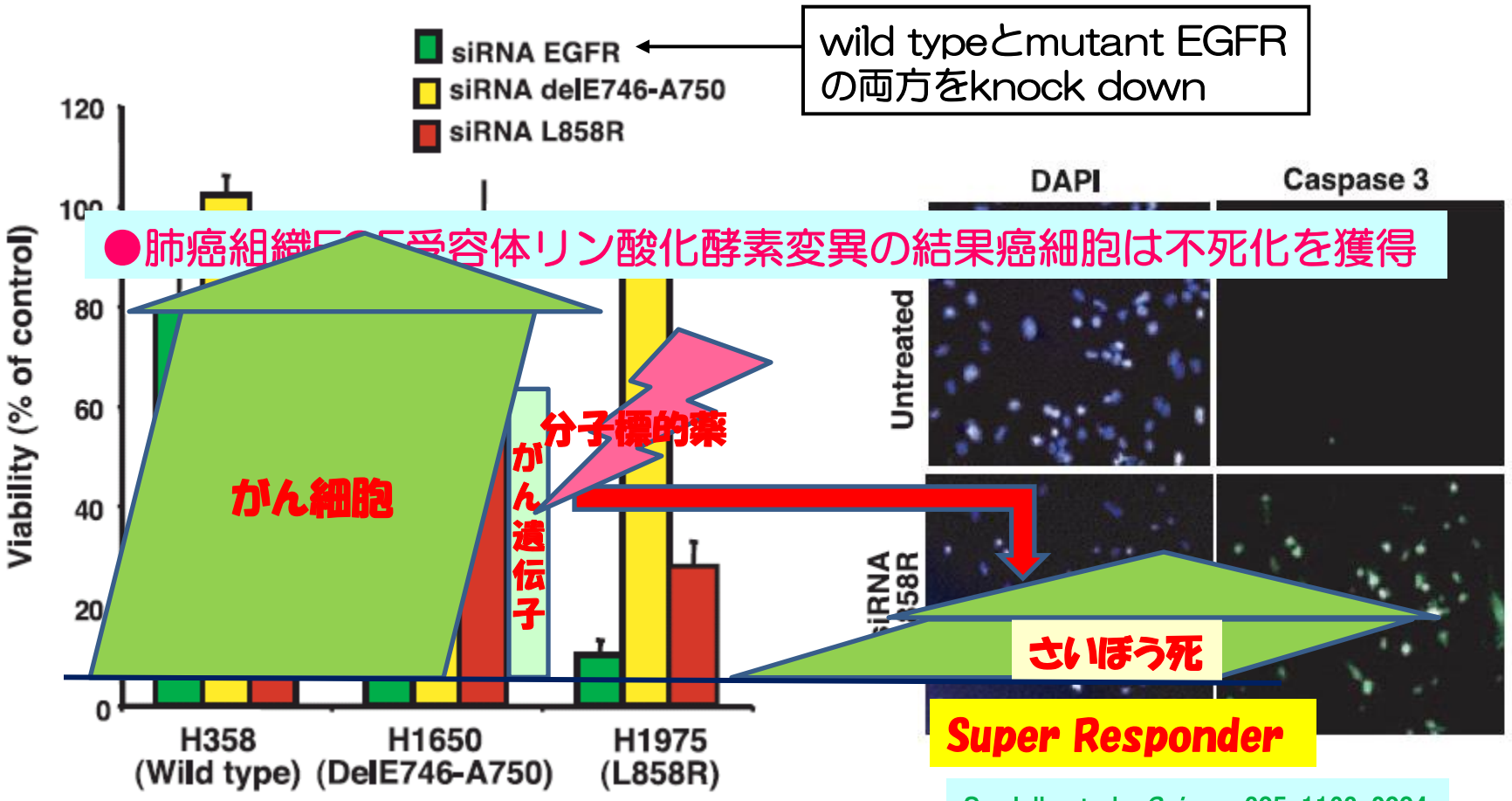
分子標的薬の薬理作用は
抗細胞死シグナル阻止だ！
（super-responder）

まさか！

Mutant EGFRでは“oncogene addiction”となって生きている

↓

そのシグナル遮断により肺腺癌はapoptosisに陥る



Sordella et al. *Science* 305, 1163, 2004

ある癌腫に特異変異が集積する？
（gefitinibは肺癌しか効かない）

まさか！

REVERSE ONCOLOGY!!

ある体細胞変異に人種差がある？
（人種ゲノム背景に肺発癌関連）

まさか！

REVERSE ONCOLOGY!!

標的薬有効なEGFR変異は女性肺腺がんの50%

		EGFR活性型変異頻度
腺癌	110/224	49％
非腺癌	1/53	（腺扁平上皮癌）2％
腺癌症例		
女性	70/113	62％
男性	40/111	36％
喫煙歴なし	76/112	68％
喫煙歴あり	34/112	31％

Kosaka et al. Cancer Res 64, 8919, 2004

女性肺腺がんの内の有効変異頻度　　奏功率

2/3　x　3/4 = 1/2

タバコを吸わない女性肺がん
５０%が分子標的薬が有効

しかもアジア人に共通

前向きEGFR変異解析研究と肺腺癌個別化医療を考える

倫理委員会に審査申請・承諾

（受付番号：２００４－１２６）

様式第４号

倫　理　委　員　会

審査結果通知書

平成１６年６月２１日

実施責任者：貫和　敏博　殿

東北大学医学部・医学系研究科
倫理委員会委員長　糸山　泰人

研究課題名：非小細胞肺癌組織における遺伝子変異にもとづくゲフィチニブの治療効果をプロスペクティブに検討する臨床試験

申請のあった上記研究計画について，審査の結果下記のとおり判定しました。

記

判定

○承認する。
条件付きで承認する。
変更を勧告する。
承認しない。
該当しない。

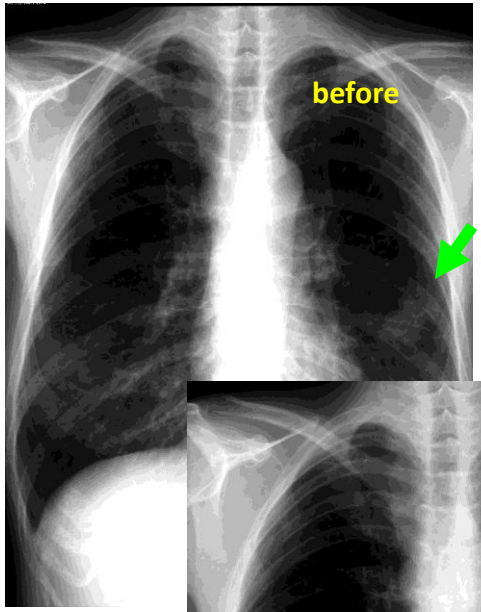
条件又は変更勧告の内容及び理由

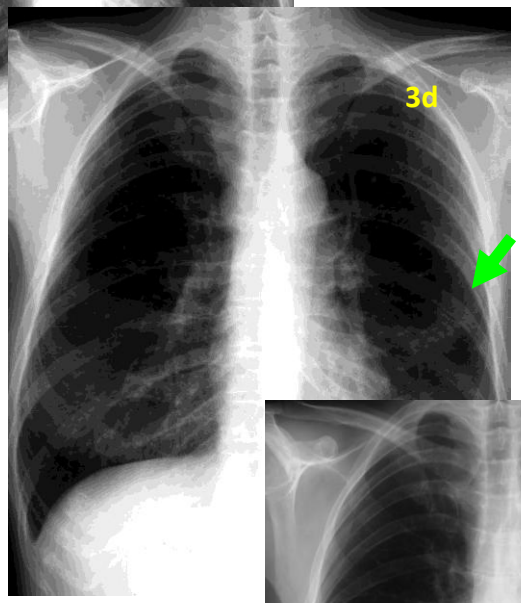
RCT のチェックリストを提出すること。

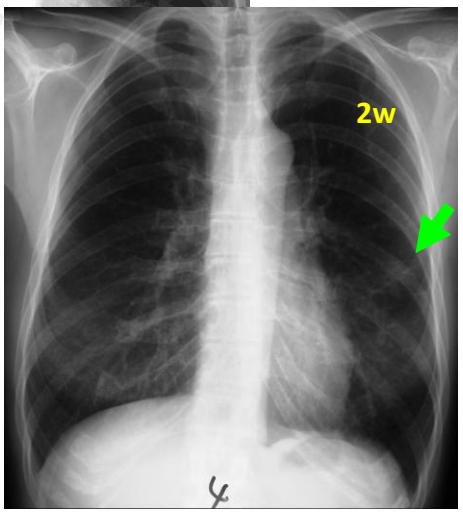
患者（53F）の肺生検・骨生検検体よりEGF受容体exon18～21の塩基配列

第21エクソンの2573番塩基のT→G変異で858番アミノ酸がロイシンからアルギニンに置換。ヘテロの読み（変異がヘテロであり、一部正常組織混入）となる。この変異は米国人にも日本人にも見つかっている。

目を見張るEGFR変異陽性者イレッサ初回投与効果：スーパーレスポンダー

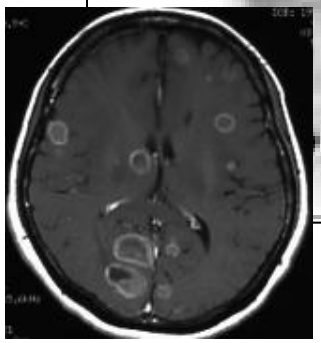


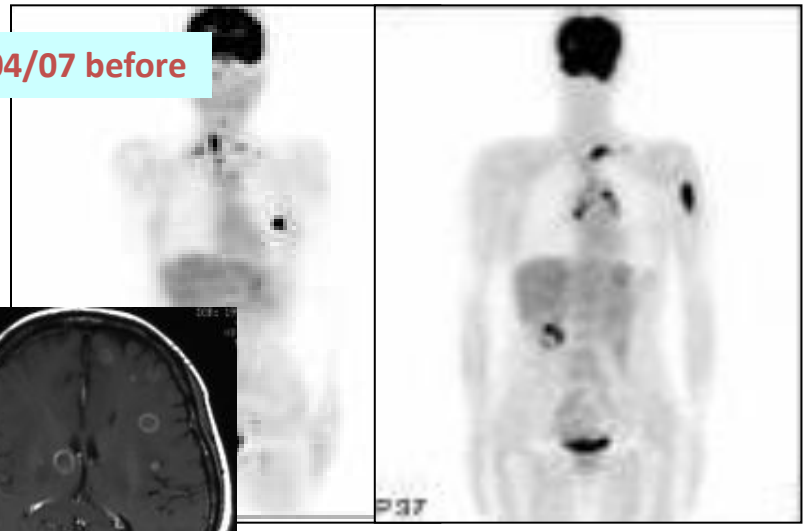




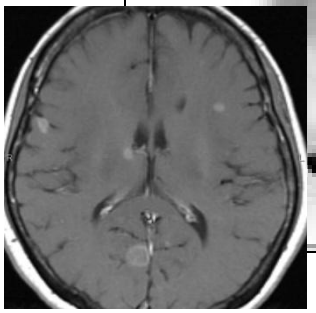
Gefitinib 250mg
Once orally

04/07 before





04/10 3m after



Deceased on 06/11/30

国内各施設から報告されたEGFR変異陽性ＮＳＣＬＣに対するゲフィチニブ初回治療のプロスペクティブ試験

	例数	奏功率	無増悪生存期間	全生存期間	発表
東北大学	16	75%	9.7 M	MST 未到達	JCO 2006
埼玉医科大学	27	78%	9.4 M	MST 15.4 M	BJC 2006
北海道臨床研究談話会	16	75%	8.9 M	MST 未到達	BJC 2006
西日本がん研究機構	28	78%	9.0 M	MST 未到達	JRC 2007
群馬大学	20	83%	12.9 M	MST 未到達	Lung Cancer 2007
愛知県がんセンター	21	91%	7.7 M	MST 未到達	JTO 2007

昨年ようやく統合解析
Clin Cancer Res. 15(13):4493-8. 2009

日常 出が可能

臨床診断用検体がそのままEGFR変異検索へ

通常の病理提出用臨床検体
（気管支鏡下生検、擦過細胞診、胸水細胞診等）

検体一部を保存

提出検体
病理診断陽性
（通常肺腺癌）

提出検体
病理診断陰性

肺癌診断再検査

保存検体を変異検索提出

肺腺癌以外の組織型は例外を除き変異検索せず

EGFR-TK活性型変異検索
定量PCR反応

反応不備
（実際には1%以下）

可能なら変異
検出再検査

変異陽性
（30-40%）

欠失型：約55%
L858R：約40%
その他活性型：約5%

前向き臨床試験対象候補

奏功率70-90%

Methods			PNA-LNA PCR clamp method	PCR-invader method	Direct sequence
Mutations in exons	exon 18	G719C	○	○	△
		G719S	○	○	△
		G719A	○	○	△
	exon 19	E746-A750del (nt2235-2249del)	○	○	△
		E746-A750del (nt2236-2250del)	○	○	△
	exon 20	L858R	○	○	△
		L851Q	○	○	△
	exon 21	T790M	○	○	△
Sensitivity			1%	1%	10 -to -20%
Samples			Cancer tissue, biopsied samples, BAL cells, brushing cells, aspiation samples, paraffin-embedded samples	Cancer tissue, biopsied samples, BAL cells, brushing cells, aspiation samples, paraffin-embedded samples	Cancer tissue, paraffin-embedded samples
Time for report			3 to 7 days	7 to 12 days	7 to 12 days
Cost (insurance)			¥20,000	¥20,000	?

A

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

Makoto Maemondo, M.D., Ph.D., Akira Inoue, M.D., Ph.D., Kunihiko Kobayashi, M.D., Ph.D., Shunichi Sugawara, M.D., Ph.D., Satoshi Oizumi, M.D., Ph.D., Hiroshi Isobe, M.D., Ph.D., Akihiko Gemma, M.D., Ph.D., Masao Harada, M.D., Ph.D., Hirohisa Yoshizawa, M.D., Ph.D., Ichiro Kinoshita, M.D., Ph.D., Yuka Fujita, M.D., Ph.D., Shoji Okinaga, M.D., Ph.D., Haruto Hirano, M.D., Ph.D., Kozo Yoshimori, M.D., Ph.D., Toshiyuki Harada, M.D., Ph.D., Takashi Ogura, M.D., Masahiro Ando, M.D., Ph.D., Hitoshi Miyazawa, M.S., Tomoaki Tanaka, Ph.D., Yasuo Saijo, M.D., Ph.D., Koichi Hagiwara, M.D., Ph.D., Satoshi Morita, Ph.D., and Toshihiro Nukiwa, M.D., Ph.D., for the North-East Japan Study Group*

ABSTRACT

BACKGROUND

Non–small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS

We randomly assigned 230 patients with metastatic, non–small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin–paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS

In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

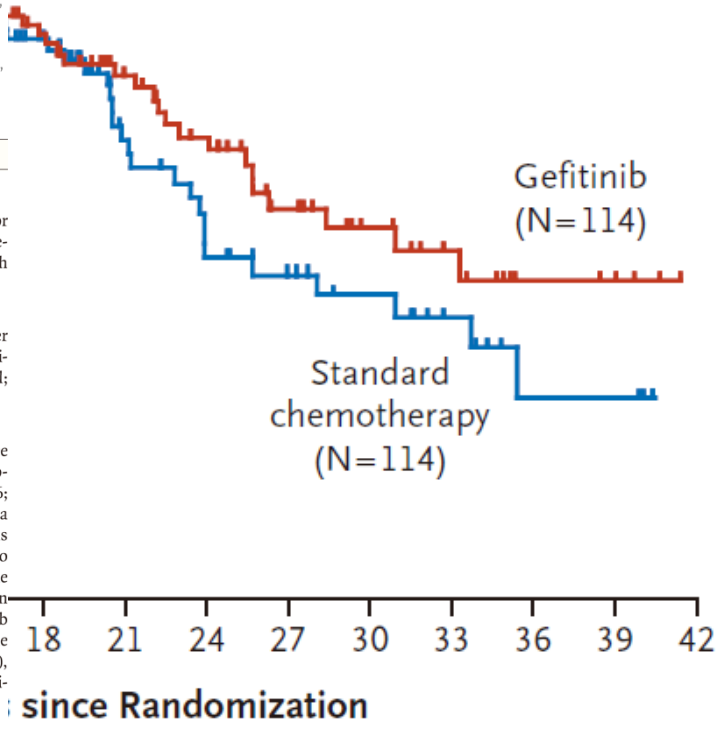
CONCLUSIONS

First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Inoue at the Department of Respiratory Medicine, Tohoku University Hospital 1-1, Seiryomachi, Aobaku, Sendai, 980-8574, Japan, or at akinoue@idac.tohoku.ac.jp.

*Contributing members of the North-East Japan Study Group are listed in the Appendix.

N Engl J Med 2010;362:2380-8.



Maemondo M et al: NEJM, 2010.

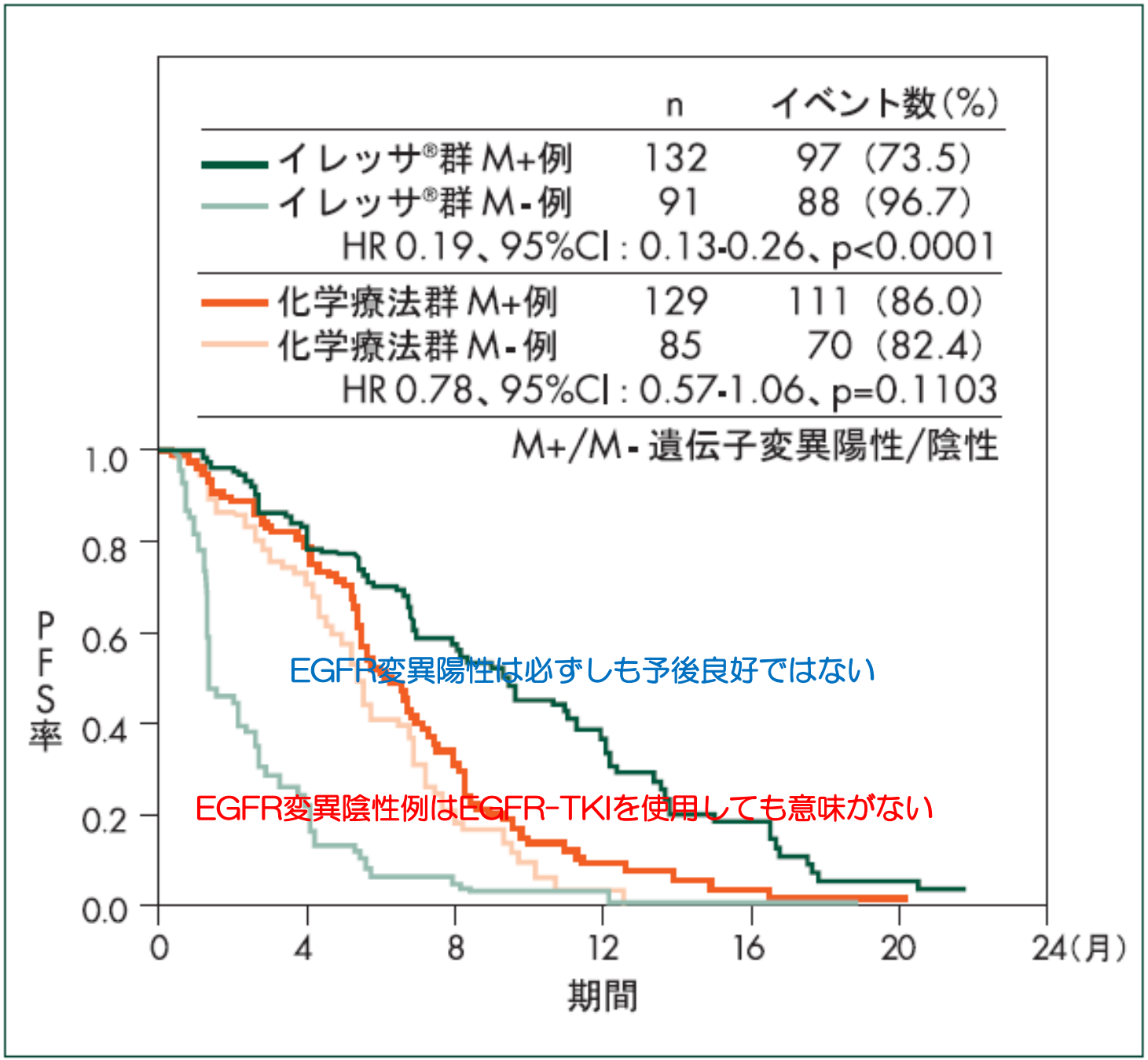
okyo, Japan

Japan (NEJ) Gefitinib Study Group

N Engl J Med. 2

Gefitinib or C
Adenocarcin
Mok TS, Wu

BACKGROUND
suggested that
efficacious in s
cancer. METHC
randomly assig
who had advan
nonsmokers or
mg per day) (60
to produce an a
per minute) plu
surface area) (6
progression-fre
progression-fre
with carboplati
objective of she
showed its sup
paclitaxel, with
intention-to-tre
death, 0.74; 95%
P<0.001). In the
for the epiderm
mutation, progr
among those w
received carbo
or death, 0.48; 9
subgroup of 17
progression-fre
those who rece
progression or
P<0.001). The n
acne (in 66.2%
gefitinib group
(67.1%), and alo
group. CONCLU
paclitaxel as an
adenocarcinom
in East Asia. Th
EGFR gene is a
gefitinib.



.48 (95% CI, 0.36–0.64)

b, 97 (73.5%); carboplatin
el, 111 (86.0%)

Gefitinib

16 20 24

ndomization

11 3 0
2 1 0

3 (95% CI, 0.58–0.81)

268 (69.4%); carboplatin
316 (80.2%)

Gefitinib

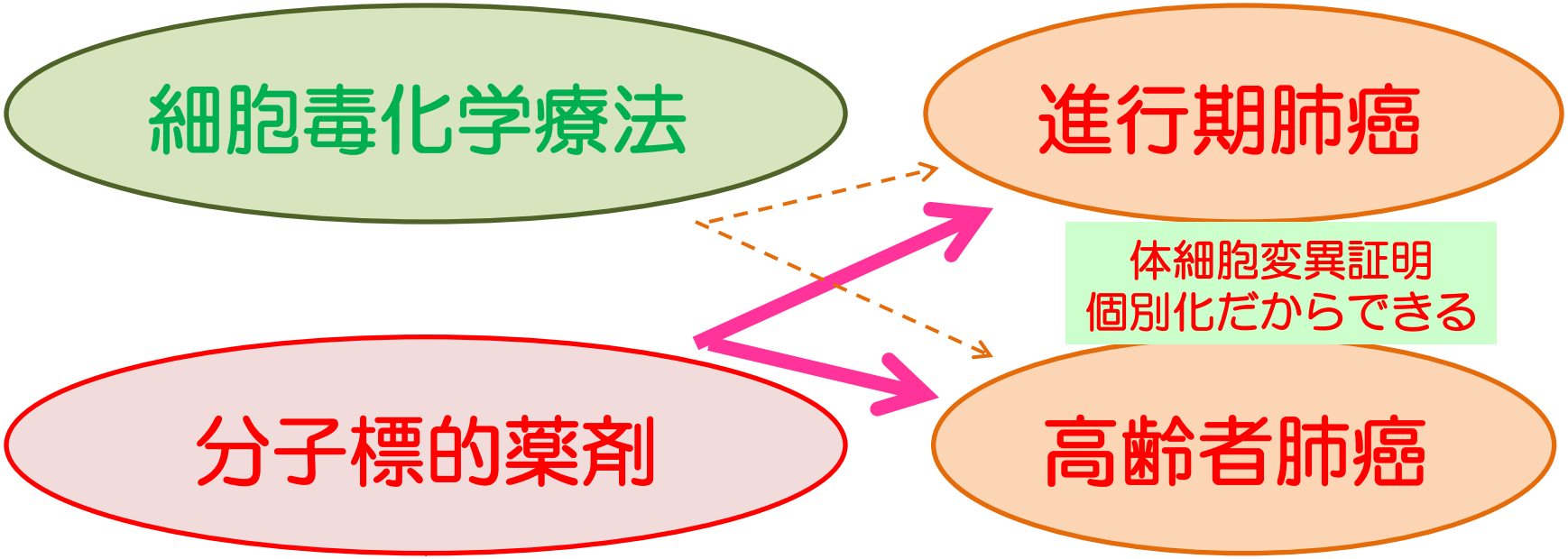
16 20 24

ndomization

12 2 0
1 0 0

ere positive for the
wn *EGFR* mutation sta-
rall population, results
en hazards are not pro-
zard ratios were calcu-
g history (nonsmoker

分子標的薬は適応を拡げる
ー進行期・高齢者ー

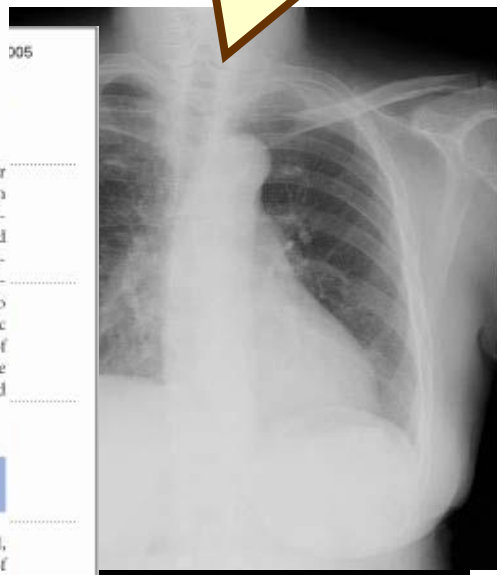


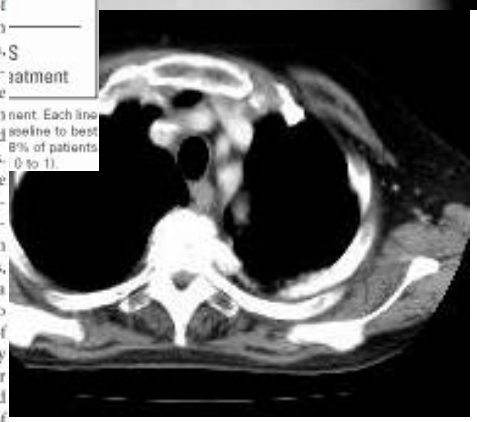
PS不良の

済第Ⅱ相試験

５０代

PS０に！





ゲフィチニブ治療

治療３ヶ月後

治るように癌の浸潤も治る

Published Ahead of Print on February 17, 2009 as 10.1200/JCO.2008.20.4859
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2008.20.4859

JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

The "Lazarus Response" in Treatment-Naïve, Poor Performance Status Patients With Non–Small-Cell Lung Cancer and Epidermal Growth Factor Receptor Mutation

Corey J. Langer, *Thoracic Oncology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

BACKGROUND: PERFORMANCE STATUS 2 PATIENTS WITH NON–SMALL-CELL LUNG CANCER

In a series of more than 500 non–small-cell lung cancer (NSCLC) patients evaluated by Cella and colleagues in quality of life studies, the prevalence of poor performance status (PS; 2 to 4) among lung cancer patients was 34% when estimated by providers and 48% when determined by patients themselves; these findings strongly suggest that physicians and nurses tend to underestimate the degree of compromise in PS.[1] Unfortunately, there is no standard therapy in advanced NSCLC patients with very poor performance status (PS 3 to 4). Median survival (MS) without therapy, which is the norm, is typically fewer than 2 to 3 months in such individuals, whether the compromise in PS is due to disease burden or comorbidity.[2,3]

The optimal nature of treatment for PS 2 patients with advanced NSCLC remains controversial.[5-7] Data from prospective phase III trials isolating the role of platinum suggest an improvement in survival for those receiving third generation platinum-based combinations compared to the constituent, nonplatinum single agent.[8,9] Lilenbaum et al, in a phase III trial, isolated the role of carboplatin in combination with paclitaxel compared to single-agent paclitaxel. They demonstrated an increase in survival for PS 2 patients receiving the combination, but the results were still dismal: 4.7 months MS for those receiving the combination compared to 2.4 months for those receiving single-agent therapy with 1-year survival rates of 19% and 10%, respectively. Virtually no PS 2 patients were alive on the single-agent arm at 2 years.[8] More recent studies suggest that modern combination regimens may be able to generate MS times of 6 to 8 months in PS 2 individuals, but seldom higher.[10,11] In Eastern Cooperative Oncology Group (ECOG) 2598, chemotherapy-naïve PS 2 patients with advanced NSCLC receiving either dose-attenuated paclitaxel and carboplatin or gemcitabine and cisplatin realized MS of 6.2 and 6.9 months, respectively, with 1-year survival rates of 19% and 25%.[10] A much larger phase III trial enrolling more than 400 patients and restricted to a PS 2 population evaluated carboplatin in combination with either paclitaxel or polyglutamated paclitaxel. The results from this trial—and, to date, the "best" results in this population—showed a MS of 7.9 months and 8.0 months, respectively, for standard versus polyglutamated paclitaxel and identical 1-year survival rates of 31%.[12]

Baseline comorbidities and anticipated toxicities are a major impediment to more aggressive therapy in poor PS patients with NSCLC. For example, work by LeChevalier et al comparing vinorelbine, either alone or in combination with cisplatin, to vindesine and cisplatin, not only failed to demonstrate a significant survival advantage in PS 2 patients receiving the cisplatin and vinorelbine combination, but also showed substantially more severe toxicity compared to the single agent.[13] Current trials are emphasizing the role of less toxic agents in the PS 2 population; but none to date, with the exception of the work by Inoue and colleagues,[14] highlighted in this issue of the *Journal of Clinical Oncology*, have assessed customized therapy based on epidermal growth factor receptor (EGFr) mutation status.

GEFITINIB IN TREATMENT-NAÏVE POOR PS PATIENTS WITH NSCLC

In this small phase II study in poor PS patients with advanced, chemotherapy-naïve NSCLC, Inoue et al report a median survival of 17.8 months for first-line EGFr tyrosine kinase inhibition (TKI) in patients with mutated tumors,[14] most of whom, by traditional criteria, would not have received systemic therapy.[1,2,5] This article is remarkable in that it included PS 3 and 4 patients, not just PS 2. Despite the fact that most of these patients had aggressive disease, treatment with gefitinib in this setting yielded a median survival three- to four-fold higher than that generally observed with conventional cytotoxics. Moreover, PS consistently improved in these patients over the course of treatment. One would assume that quality of life (QOL) also improved, although confirmatory QOL data are not provided. The authors also make it clear that a substantial proportion of those with EGFr mutation did not fit the typical clinical profile; in other words, they were not necessarily female, nonsmokers with adenocarcinoma histology. The relatively low percentage of patients who went on to receive second-line therapy with conventional cytotoxics at the time of disease progression seems curious, if not bothersome, particularly when these individuals, whether they received additional treatment or not, lived an average of one year beyond the time of documented progressive disease (PD). Assuming there is no under-reporting of second-line treatment, this observation would suggest that refractory

From the North East Japan Study Group, Tohoku University, Graduate School of Medicine and School of Medicine; Miyagi Cancer Center, Kesennuma City Hospital, Miyagi; Saitama Medical University, Saitama; Kanto Medical Center NTT EC; Nippon Medical School, Tokyo; Tsubol Cancer Center Hospital, Fukushima, Hokkaido University, Graduate School of Medicine, Hokkaido; Yokohama City University, Kanagawa, Japan.

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Written on behalf of the North East Japan Gefitinib Study Group.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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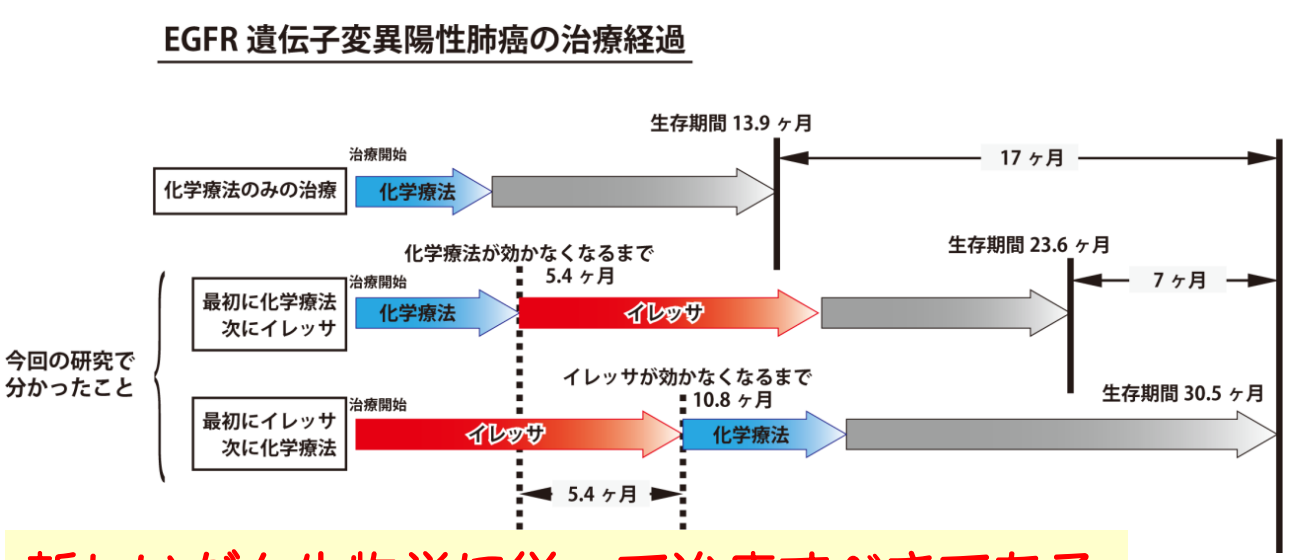
0732-183X/09/2799-1/$20.00

DOI: 10.1200/JCO.2008.19.7958

EGFR活性型体細胞変異陽性者への個別化標的医療の意味は？

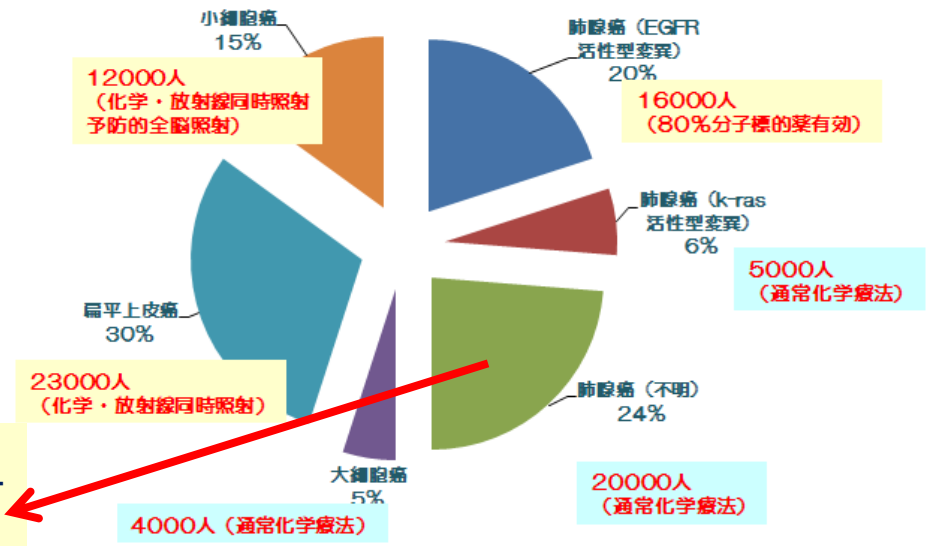


2010年肺癌死
男：50,369人
女：19,409人
計：69,769人

推計罹患者：90000人

新しいがん生物学に従って治療すべきである

肺癌組織型分類と治療対応



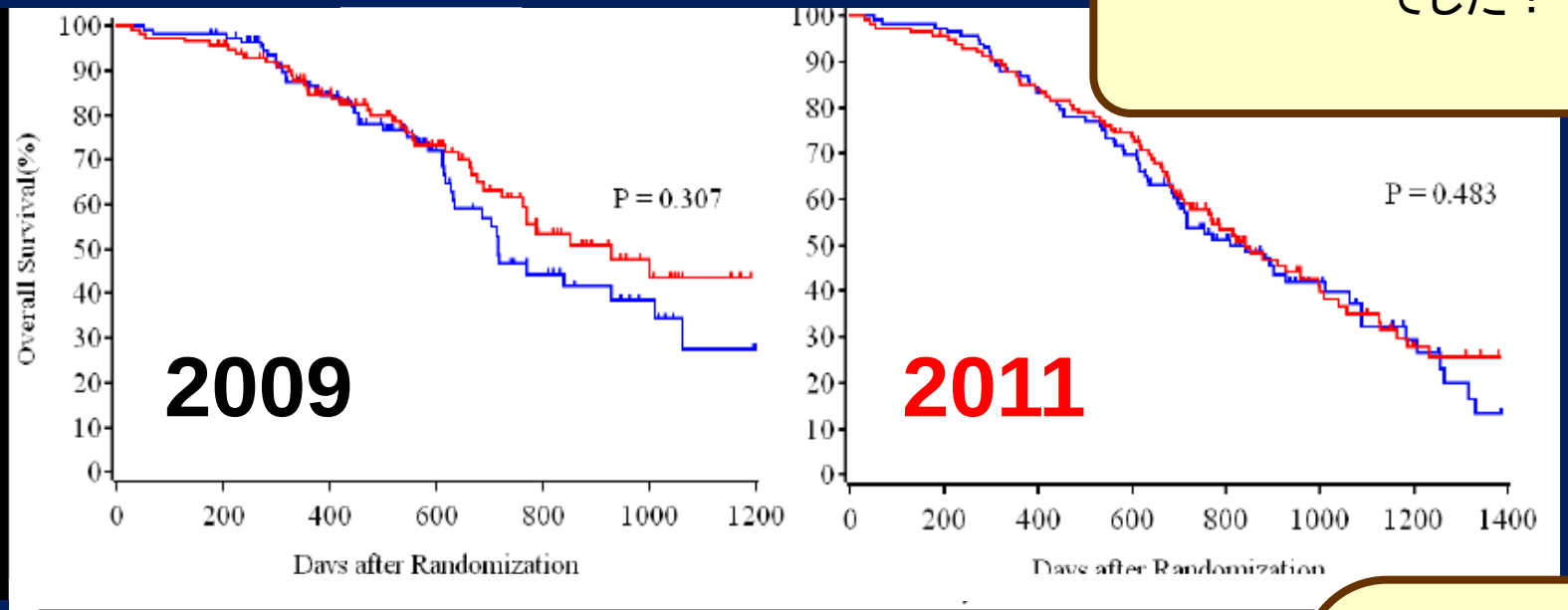
この治療の恩恵を被る人
●女性肺癌患者（肺腺癌）の
2/3（陽性）ｘ3/4（奏功）で
（5年生存率20%で概算23000人の約50%）
10000人/年
●男性肺腺癌患者もほぼ同数なら
全肺癌患者の
20000人/年

Nature. 2007 Aug 2;448(7153):561-6.
Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer.
Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Jichi Medical University, Tochigi 329-0498, Japan.

この結果に対して否定的な声も耳にしますが

NEJ002の最終OS解析（PD#7519）

おかげさまでポスター前は大盛況でした！



	2009		2011	
	Gefitinib	CBDCA/PTX	Gefitinib	CBDCA/PTX
Median OS (mo)	30.5	23.6	27.7	26.6
Hazard ratio (95%CI)	0.798 (0.517-1.232)		0.887 (0.634-1.241)	
1-year OS rate	84.7%	86.4%	85.0%	86.8%
2-years OS rate	61.4%	46.7%	57.9%	53.7%
Number of Event	39	43	69	69

死亡イベント割合が36%から61%になり、より信頼性が高い結果です

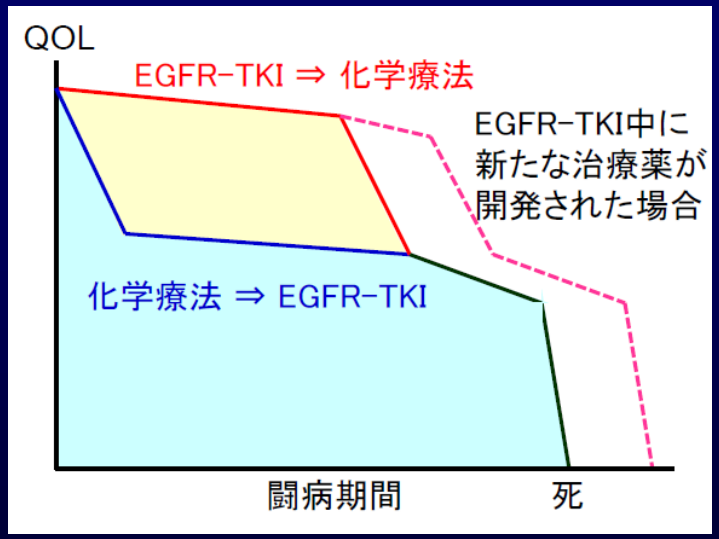
私としてはOSがくっついた点は全く気になりません

何故ならそうなって当たり前だからです

	Gefitinib	CBDCA/PTX
EGFR-TKI	100%	98.2%
Gefitinib	100%	98.2%
Erlotinib	27.2%	28.9%
BIBW2992	0	1.8%
Chemotherapy	71.9%	100%
Platinum based	64.9%	100%
CBDCA/PTX	50.0%	100%
Pemetrexed	28.9%	15.8%
Docetaxel	24.6%	19.3%
Others	23.7%	22.8%

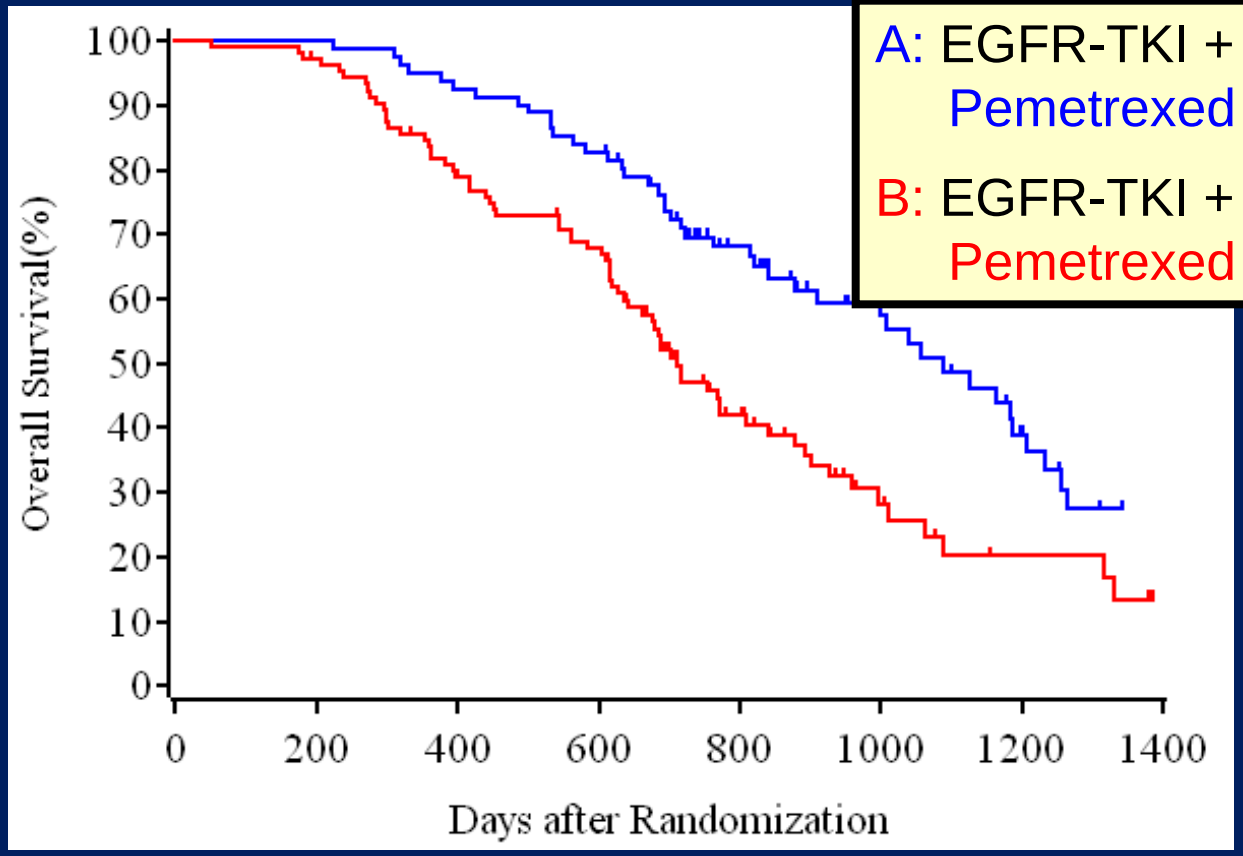
NEJ002のケモ群では、ほぼ全例がイレッサにクロスオーバーされている（他に類を見ない高率）でも、実臨床でこれを再現できる自信は？

論理的に考えて、奏効率が高く、効果も長く持続して、QOLに優れ、完璧に治療されたケモ群にも負けてない初回イレッサを否定できる？（治療初期に良い全身状態を保てれば新薬を試せる機会も増える）



イレッサかケモを選べと言われたら、イレッサを優先すべき

その一方で、さらなる向上を期待させるデータ



A: EGFR-TKI + Platinum with Pemetrexed or Docetaxel (n=81)

B: EGFR-TKI + Platinum without Pemetrexed and Docetaxel (n=105)

Median OS

A: 35.8 months

B: 23.4 months

P<0.001

あくまで事後解析ですが…

結果的にEGFR-TKI、プラチナ、アリムタ（またはドセ）を全て使い切った患者さんのMSTは何と3年にまで延びる！

これこそまさにNEJ005で検討している内容です

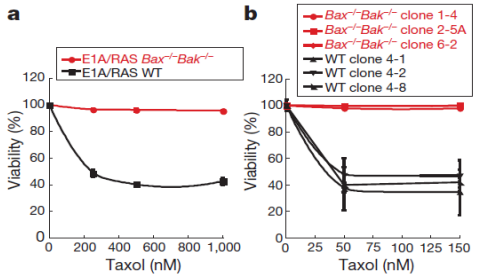
なぜTaxaneは単剤でもあんなに効くのか？答えはAnti-antiapoptosis

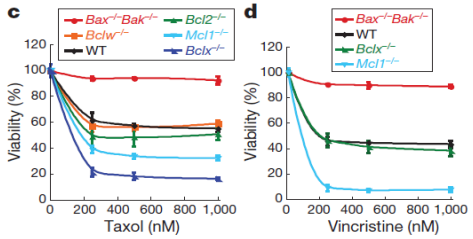
LETTER

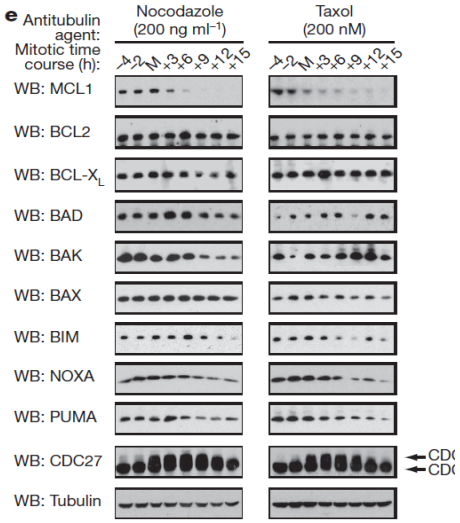
Nat. 471, 110, 2011

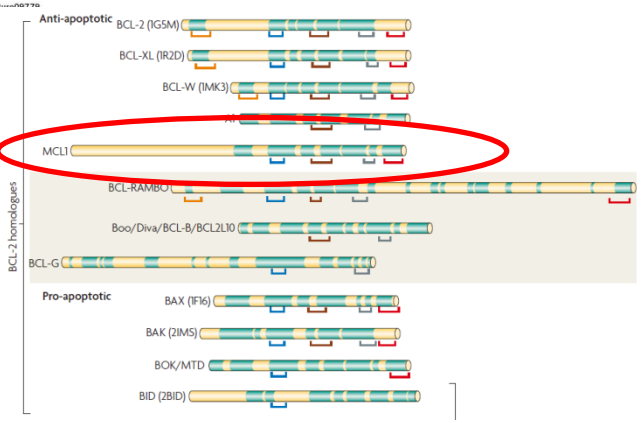
Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7

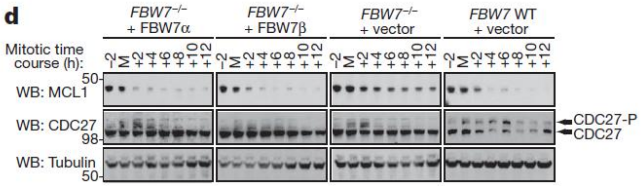
Ingrid E. Wertz[2], Saritha Kusam[1], Cynthia Lam[1]*, Toru Okamoto[2]*, Wendy Sandoval[3], Daniel J. Anderson[4], Elizabeth H James A. Ernst[1,3], Mike Eby[4], Jinfeng Liu[5], Lisa D. Belmont[4], Joshua S. Kaminker[5], Karen M. O'Rourke[6], Kanan Pujara[2] Pawan Bir Kohli[6], Adam R. Johnson[6], Mark L. Chiu[2], Jennie R. Lill[3], Peter K. Jackson[4], Wayne J. Fairbrother[1], Somasekar Seshagiri[2], Mary J. C. Ludlam[1], Kevin G. Leong[4], Erin C. Dueber[1], Heather Maecker[4], David C. S. Huang[2,10] & Vishva M. Dixit[6]



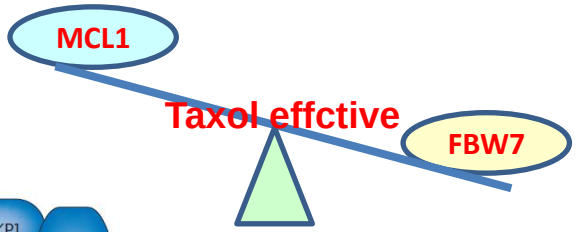




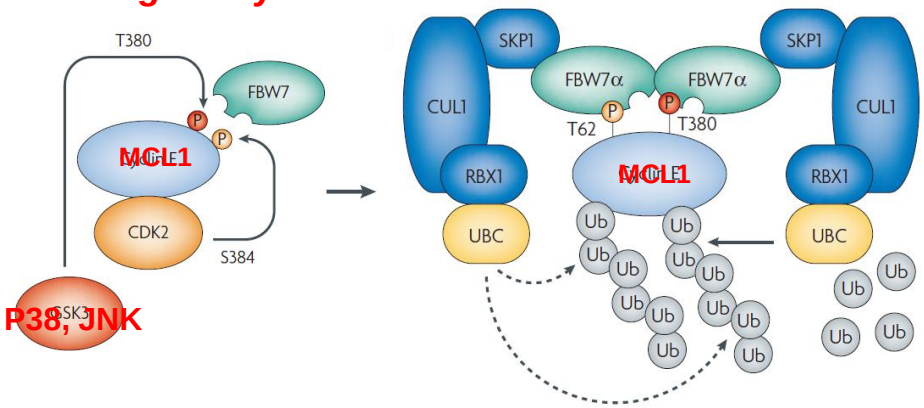




Microtubules have pivotal roles in fundamental cellular processes and are targets of antitubulin chemotherapeutics[1]. Microtubule-targeted agents such as Taxol and vincristine are prescribed widely for various malignancies, including ovarian and breast adenocarcinomas, non-small-cell lung cancer, leukaemias and lymphomas[1]. These agents arrest cells in mitosis and subsequently induce cell death through poorly defined mechanisms[2]. The strategies that resistant tumour cells use to evade death induced by antitubulin agents are also unclear[2]. Here we show that the pro-survival protein MCL1 (ref. 3) is a crucial regulator of apoptosis triggered by antitubulin chemotherapeutics. During mitotic arrest, MCL1 protein levels decline markedly, through a post-translational mechanism, potentiating cell death. Phosphorylation of MCL1 directs its interaction with the tumour-suppressor protein FBW7, which is the substrate-binding component of a ubiquitin ligase complex. The polyubiquitylation of MCL1 then targets it for proteasomal degradation. The degradation of MCL1 was blocked in patient-derived tumour cells that lacked *FBW7* or had loss-of-function mutations in *FBW7*, conferring resistance to antitubulin agents and promoting chemotherapeutic-induced polyploidy. Additionally, primary tumour samples were enriched for *FBW7* inactivation and elevated MCL1 levels, underscoring the prominent roles of these proteins in oncogenesis. Our findings suggest that profiling the FBW7 and MCL1 status of tumours, in terms of protein levels, messenger RNA levels and genetic status, could be useful to predict the response of patients to antitubulin chemotherapeutics.



E3 ligase system



がん治療を考え直す
抗細胞死因子除去

日本でのCBDCA＋PEMの成績は

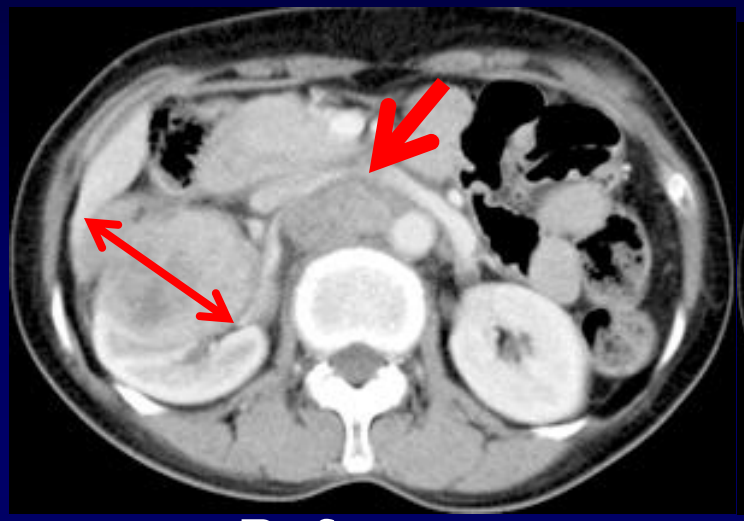
CBDCA（AUC5-6）+PEM（500 mg/m2）のPhase Ⅰ

	AUC 5 (N=5)	AUC 6 (N=14)	Total (N=19)
CR	0	0	0
PR	4	8	12
SD	0	4	4
PD	1	1	2
NE	0	1	1
RR	80.0%	57.1%	63.2%
95%CI	-	28.9-82.3%	38.4-83.7%
DCR	80.0%	85.7%	84.2%

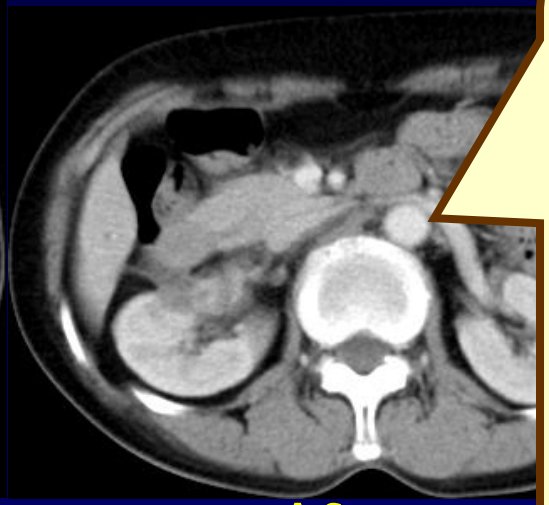
少数例の検討ではありますが、十分な有効性を感じます
（CBDCAの用量については基本的にAUC 6でOK）

CBDCA＋PEMが著効した一例

67歳女性（腺癌、EGFR変異陽性例）に対して、二次治療として
CBDCA（AUC 6.0）＋PEM（500 mg/m2）を施行

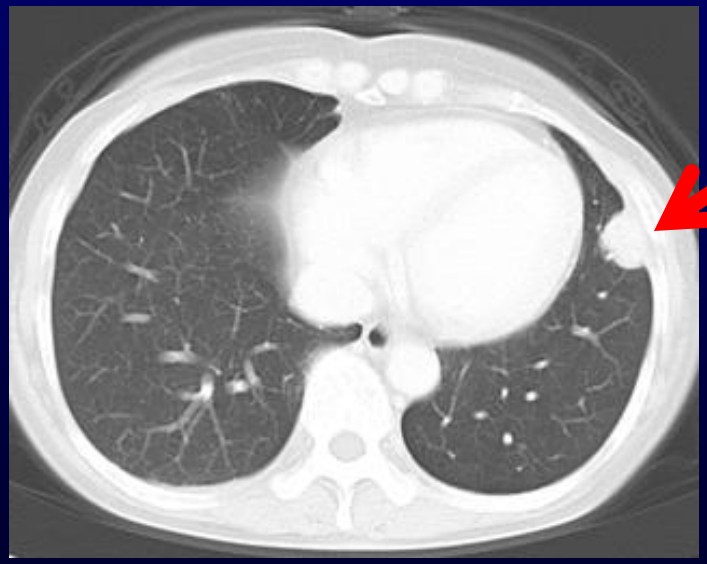


Before



After

4コース後、ほぼCRの効果。副作用はGrade3の好中球減少、貧血、血小板減少を一時的に認めるも患者さん自身はほとんど不快な症状を自覚せず



その後、PEM維持療法に移行し、現在も順調に治療中

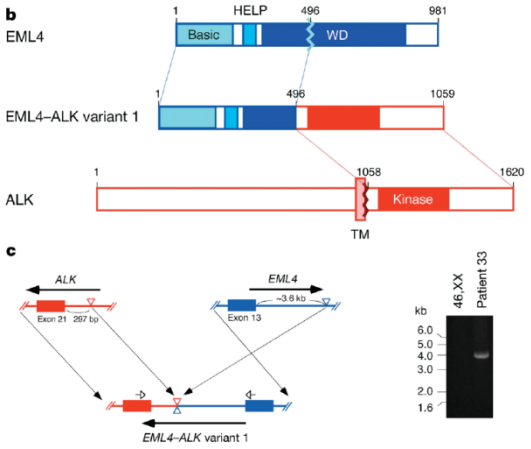
doi:10.1038/nature05945 nature

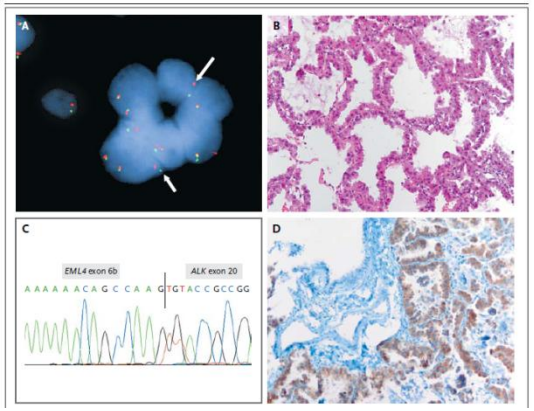
ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[3], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[4], Hiroyuki Aburatani[5–7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

Improvement in the clinical outcome of lung cancer is likely to be achieved by identification of the molecular events that underlie its pathogenesis. Here we show that a small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*) gene in non-small-cell lung cancer (NSCLC) cells. Mouse 3T3 fibroblasts forced to express this human fusion tyrosine kinase generated transformed foci in culture and subcutaneous tumours in nude mice. The *EML4–ALK* fusion transcript was detected in 6.7% (5 out of 75) of NSCLC patients examined; these individuals were distinct from those harbouring mutations in the epidermal growth factor receptor gene. Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC.





The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

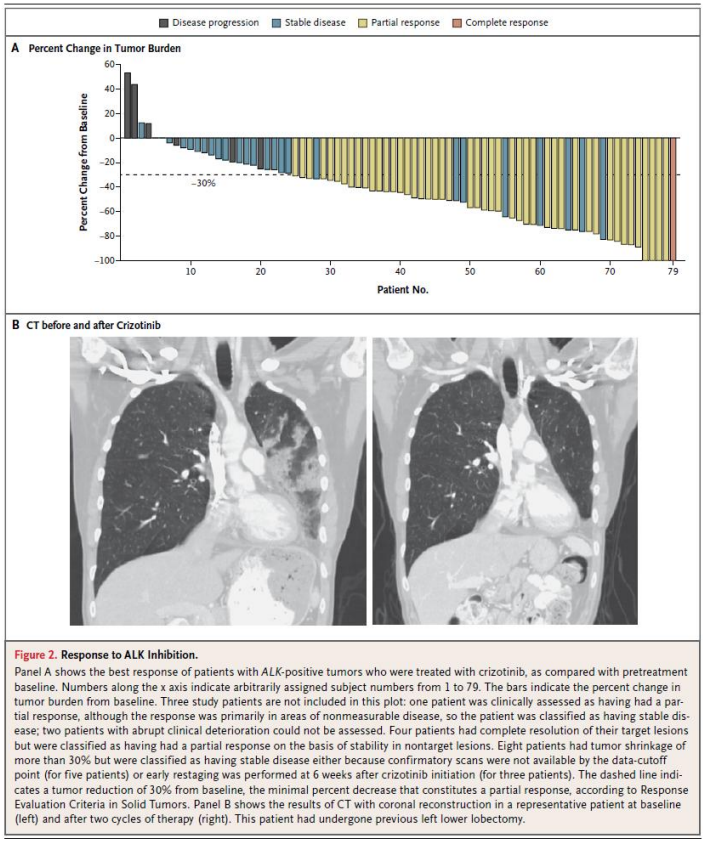


Figure 2. Response to ALK Inhibition.

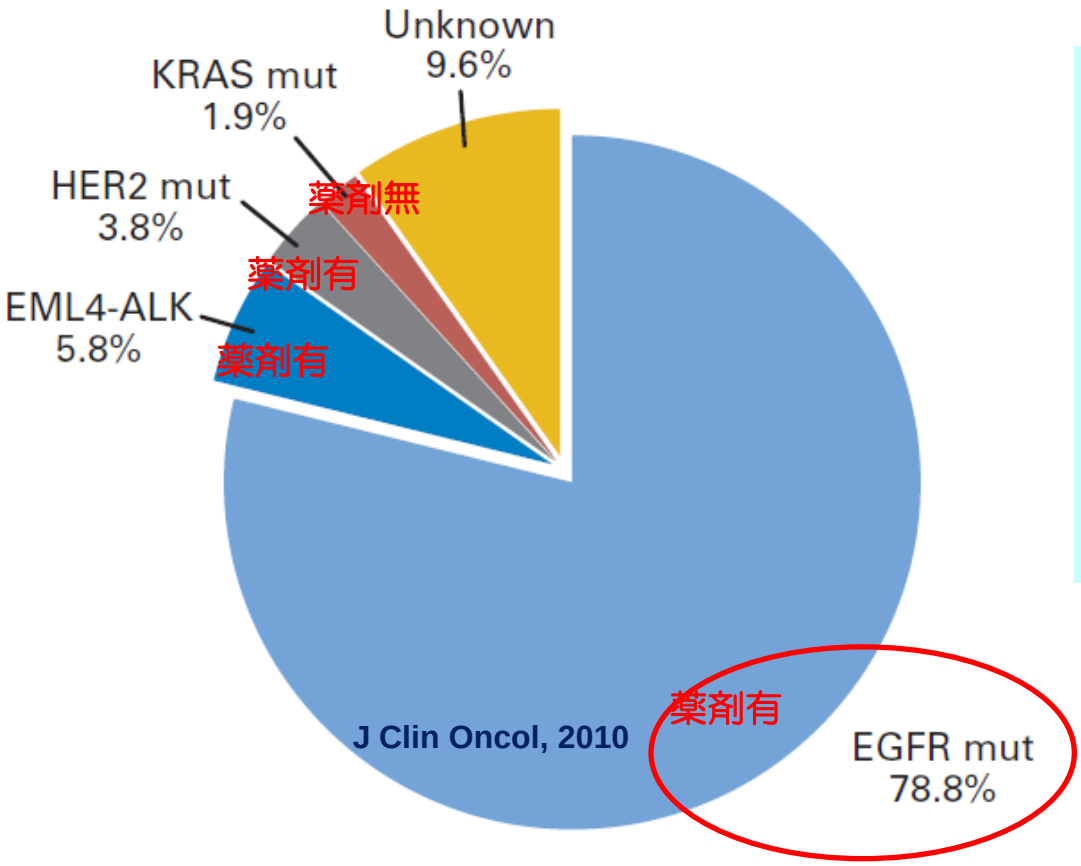
Panel A shows the best response of patients with *ALK*-positive tumors who were treated with crizotinib, as compared with pretreatment baseline. Numbers along the x axis indicate arbitrarily assigned subject numbers from 1 to 79. The bars indicate the percent change in tumor burden from baseline. Three study patients are not included in this plot: one patient was clinically assessed as having had a partial response, although the response was primarily in areas of nonmeasurable disease, so the patient was classified as having stable disease; two patients with abrupt clinical deterioration could not be assessed. Four patients had complete resolution of their target lesions but were classified as having had a partial response on the basis of stability in nontarget lesions. Eight patients had tumor shrinkage of more than 30% but were classified as having stable disease either because confirmatory scans were not available by the data-cutoff point (for five patients) or early restaging was performed at 6 weeks after crizotinib initiation (for three patients). The dashed line indicates a tumor reduction of 30% from baseline, the minimal percent decrease that constitutes a partial response, according to Response Evaluation Criteria in Solid Tumors. Panel B shows the results of CT with coronal reconstruction in a representative patient at baseline (left) and after two cycles of therapy (right). This patient had undergone previous left lower lobectomy.

●なぜ日本で発見された変異の臨床試験が日本でできないか？

●なぜ韓国ソウル大学に日本人患者を送ったのか？

運転士変異と乗客変異：分子標的薬剤

非喫煙者肺腺癌患者（中国人）の
主要ドライバー変異は90%まで判明

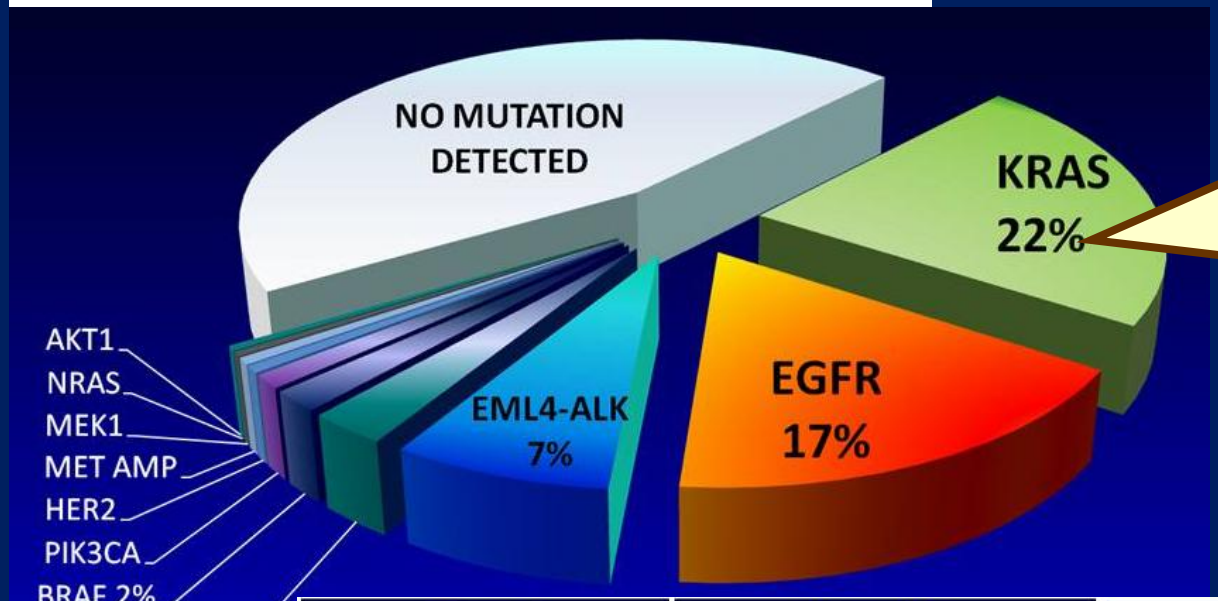


●肺癌治療は分子標的薬の開発と選択.

●今後の課題：

1. 喫煙者肺癌に対する適切な分子標的の開発.
2. 耐性克服への新規治療.
3. 肺発現への背景ゲノム検索

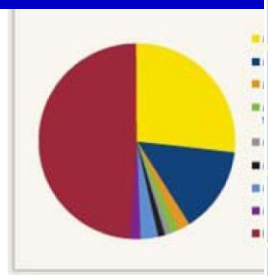
Lung Cancer Mutation Consortium: NSCLC/Drivers



遺伝子変異は54%（280/516）に認められ、97%が相互排他的であった

Target	Agent(s)
EGFR	Erlotinib + OSI 906 Erlotinib + MM 121
KRAS	Tivantinib + Erlotinib GSK1120212
MET Amplification	
EML4-ALK	Crizotinib
NRAS	GSK1120212

Target	Agent
MEK1	GSK1120212
BRAF (V600E)	GSK2118434
BRAF (not V600E)	GSK1120212
HER2	Afatinib
PIK3CA	BKM120
AKT1	



summary of the genetic testing a
of the expected 1,000 cases hav
the genes tested. There will be p
the World Conference on Lung C

With the finding that lung cancer mortality can be reduced by 20% or more by annual spiral CT scans in high-risk subjects as well as [illegible] improvements in therapy, which can [illegible] continued reduction in lung cancer mortality, attributable to scientific advances.

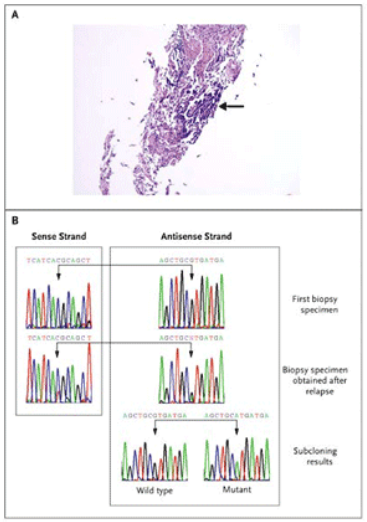
さらに魅力的なのは各対象に治療法が用意されていること

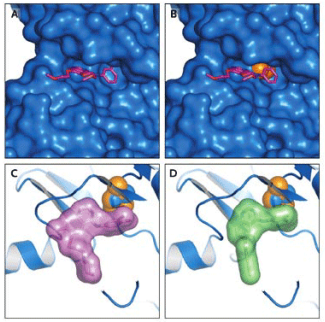
約半数の耐性機構は？

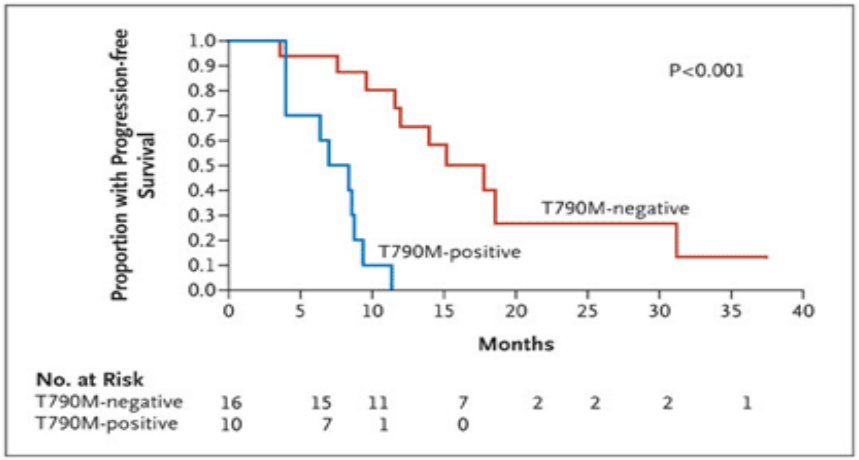
N Engl J Med. 2005 Feb 24;352(8):786-92.

EGFR mutation and resistance of non-small-cell lung cancer to gefitinib.

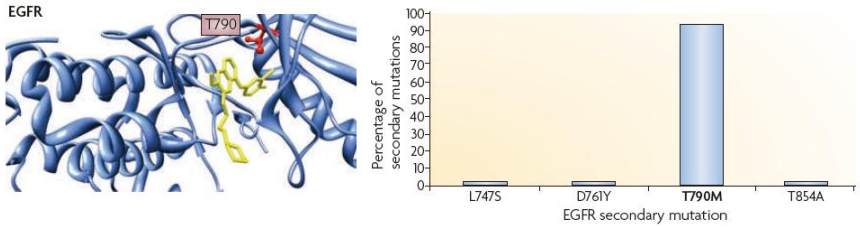
Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B.







(Haber et al NEJM, 2008)



T790M is detected in an analysis of the gefitinib resistant case

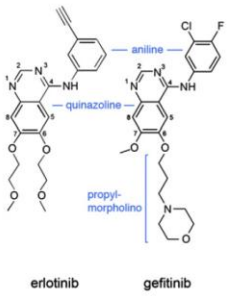
Structural change in kinase domain causes resistant, the same structural mutation resistant to Imatinib in cases of CML.

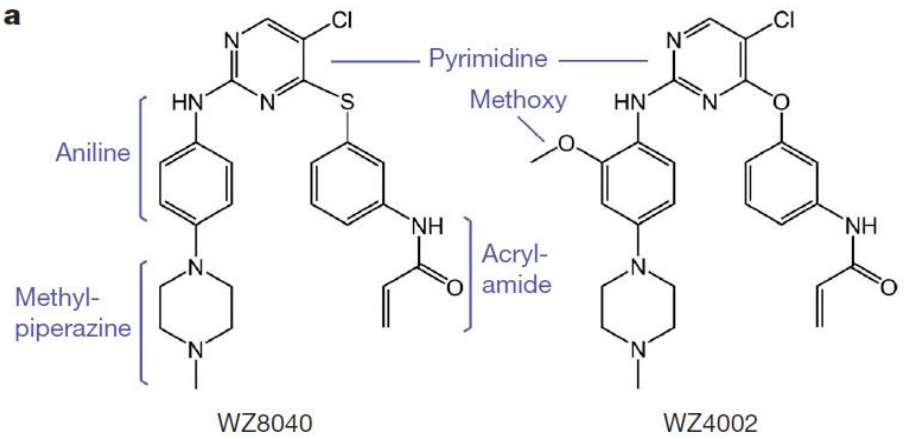
Novel mutant-selective EGFR kinase inhibitors against EGFR T790M

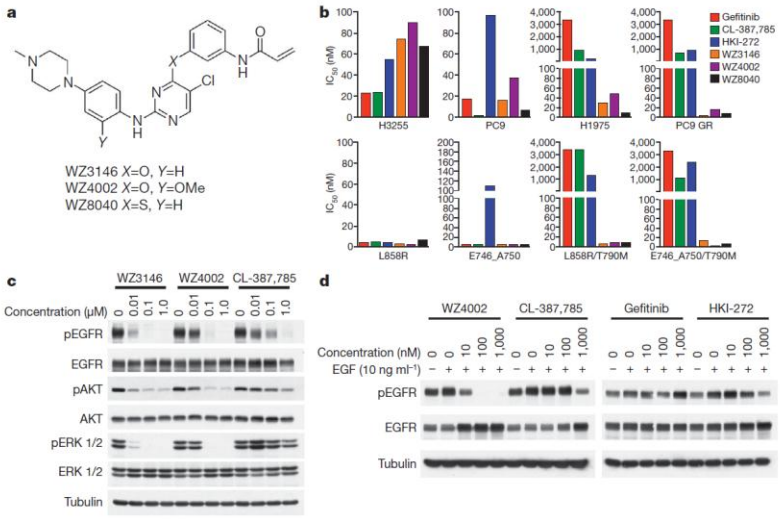
Vol 462|24/31 December 2009|doi:10.1038/nature08622

Wenjun Zhou[1,2]*, Dalia Ercan[3,4]*, Liang Chen[3,4]*, Cai-Hong Yun[1,2]*, Danan Li[3,4], Marzia Capelletti[3,4], Alexis B. Cortot[3,4], Lucian Chirieac[5], Roxana E. Iacob[6,7], Robert Padera[5], John R. Engen[6,7], Kwok-Kin Wong[3,4,8,9], Michael J. Eck[1,2], Nathanael S. Gray[1,2] & Pasi A. Jänne[3,4,8]

The clinical efficacy of epidermal growth factor receptor (EGFR) kinase inhibitors in *EGFR*-mutant non-small-cell lung cancer (NSCLC) is limited by the development of drug-resistance mutations, including the gatekeeper T790M mutation[1–3]. Strategies targeting EGFR T790M with irreversible inhibitors have had limited success and are associated with toxicity due to concurrent inhibition of wild-type EGFR[4,5]. All current EGFR inhibitors possess a structurally related quinazoline-based core scaffold and were identified as ATP-competitive inhibitors of wild-type EGFR. Here we identify a covalent pyrimidine EGFR inhibitor by screening an irreversible kinase inhibitor library specifically against EGFR T790M. These agents are 30- to 100-fold more potent against EGFR T790M, and up to 100-fold less potent against wild-type EGFR, than quinazoline-based EGFR inhibitors *in vitro*. They are also effective in murine models of lung cancer driven by EGFR T790M. Co-crystallization studies reveal a structural basis for the increased potency and mutant selectivity of these agents. These mutant-selective irreversible EGFR kinase inhibitors may be clinically more effective and better tolerated than quinazoline-based inhibitors. Our findings demonstrate that functional pharmacological screens against clinically important mutant kinases represent a powerful strategy to identify new classes of mutant-selective kinase inhibitors.







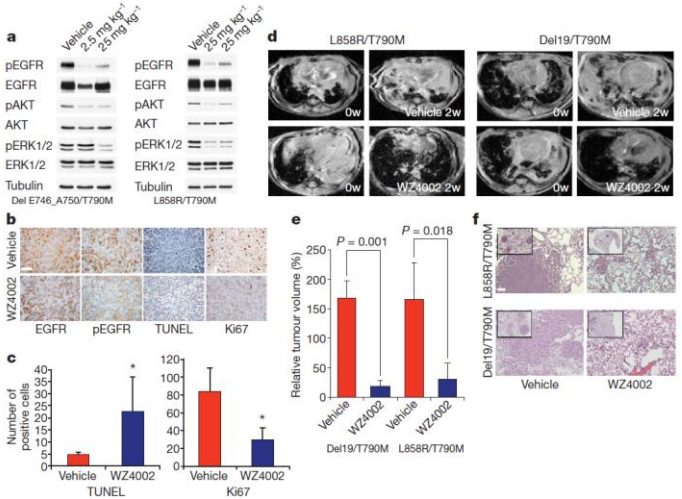


Figure 4 | WZ4002 inhibits EGFR phosphorylation and induces significant tumour regression in murine models of *EGFR* T790M. **a**, Two doses separated by 16 h of WZ4002 (2.5 mg kg^{-1} or 25 mg kg^{-1}) or vehicle were administered to EGFR delE746_A750/T790M or L858R/T790M mice with MRI-confirmed tumours. The mice were killed, the lungs isolated, grossly dissected and subjected to cell lysis. Cell extracts were immunoblotted to detect the indicated proteins. **b**, Immunohistochemical analyses of tumours from EGFR delE746_A750/T790M mice from **a** using indicated antibodies. Scale bar, 50 μm. **c**, Quantification of TUNEL- and Ki67-positive cells from tumour nodules ($n = 4$) from vehicle- and WZ4002-treated mice. The means and standard deviations are plotted. *, $P < 0.05$. **d**, MRI images of vehicle- or WZ4002-treated mice at baseline (0 weeks: 0w) and after 2 weeks (2w) of treatment. **e**, Quantification of the relative tumour volume from MRI images from vehicle-treated mice (E746_A750/T790M ($n = 3$); L858R/T790M ($n = 4$)), and WZ4002-treated L858R/T790M ($n = 3$) and E746_A750/T790M ($n = 3$) mice. The means and standard deviations are plotted. **f**, Tumours from vehicle- and WZ4002-treated mice stained with haematoxylin and eosin. Low-power view (inset) demonstrates near-complete resolution of tumours in the WZ4002-treated mice. Scale bar, 100 μm.

J Clin Invest. 2009 Oct;119(10):3000-10.

Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer.

Regales L, Gong Y, Shen R, de Stanchina E, Vivanco I, Goel A, Koutcher JA, Spassova M, Ouerfelli O, Mellinghoff IK, Zakowski MF, Politi KA, Pao W.

また新しい癌治療の可能性：不可逆性EGFR-TK阻害剤＋抗EGFR抗体

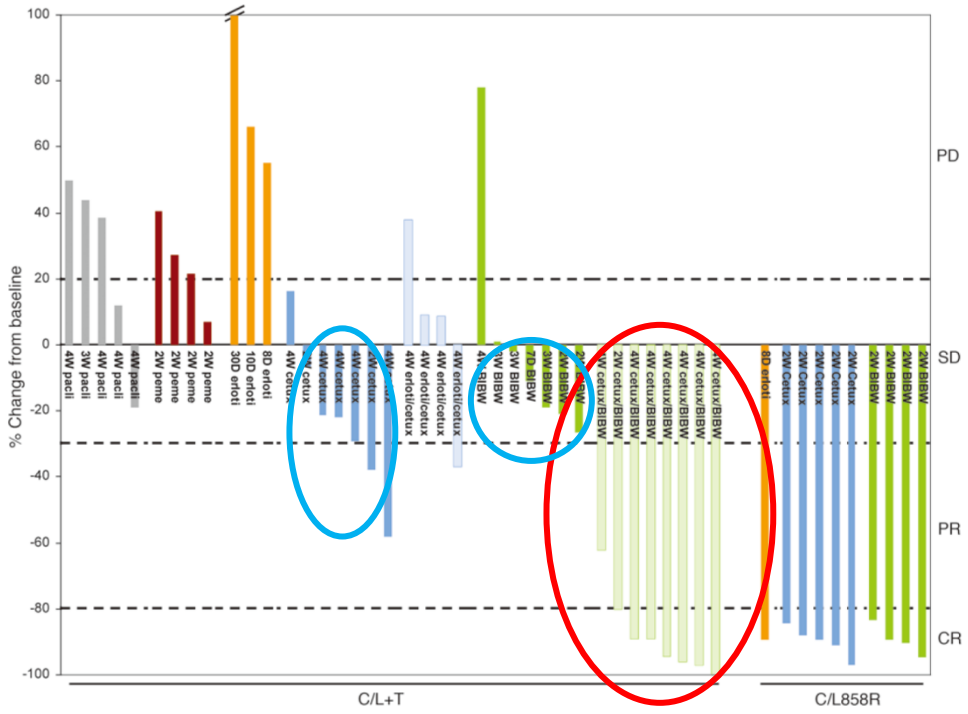


Figure 4
Change in radiographic tumor volume from baseline by treatment for individual lung tumor-bearing C/L858R and C/L+T animals. Graphed is the percentage change in tumor volume, calculated for individual animals pretreatment and after treatment with paclitaxel (pacli), pemetrexed (peme), erlotinib, cetuximab, BIBW-2992, or combinations of erlotinib or BIBW-2992 with cetuximab. Cutoffs of 20% growth, 30% shrinkage, and 80% shrinkage (dotted lines) are shown to delineate PD, PR, and CR, respectively. Mice that displayed less than 20% growth and less than 30% shrinkage in tumor volume were considered to have SD (see Methods for details.) Statistical significance (calculated using Fisher's exact test) of BIBW-2992/cetuximab–induced CRs in C/L+T animals versus paclitaxel ($P = 0.0047$), pemetrexed ($P = 0.01$), erlotinib ($P = 0.02$), cetuximab ($P = 0.001$), and cetuximab/erlotinib ($P = 0.01$).

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Full Text View | Tabular View | No Study Results Posted | Related Studies

Trial of BIBW 2992 + Cetuximab in Non-Small Cell Lung Cancer

This study is currently recruiting participants.
Verified by Boehringer Ingelheim Pharmaceuticals, September 2010

First Received: March 10, 2010 Last Updated: September 14, 2010 History of Changes

Sponsor:	Boehringer Ingelheim Pharmaceuticals
Information provided by:	Boehringer Ingelheim Pharmaceuticals
ClinicalTrials.gov Identifier:	NCT01090011

Purpose

The primary objective of this trial is to determine the maximum tolerated dose (MTD) and recommended Phase II doses for the combination of BIBW 2992 and cetuximab in patients with non-small cell lung cancer and acquired resistance to erlotinib or gefitinib.

Overall safety, pharmacokinetics and anti-tumor activity will be evaluated as secondary objectives.

Condition	Intervention	Phase
Carcinoma, Non-Small-Cell Lung	Drug: BIBW 2992 plus cetuximab	Phase I

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Phase Ib Open Label Clinical Trial of Continuous Once Daily Oral Treatment Using BIBW 2992 Plus Cetuximab (Erbitux®) in Patients With Non-small Cell Lung Cancer With Progression Following Prior Erlotinib (Tarceva®)

Resource links provided by NLM:

MedlinePlus related topics: Cancer Lung Cancer

Drug Information available for: Cetuximab BIBW 2992

U.S. FDA Resources

Further study details as provided by Boehringer Ingelheim Pharmaceuticals:

Primary Outcome Measures:

- The primary endpoint is the occurrence of dose limiting toxicity (DLT).
  [Time Frame: from day 1 treatment until first documented progression or undue toxicity]
  [Designated as safety issue: Yes]

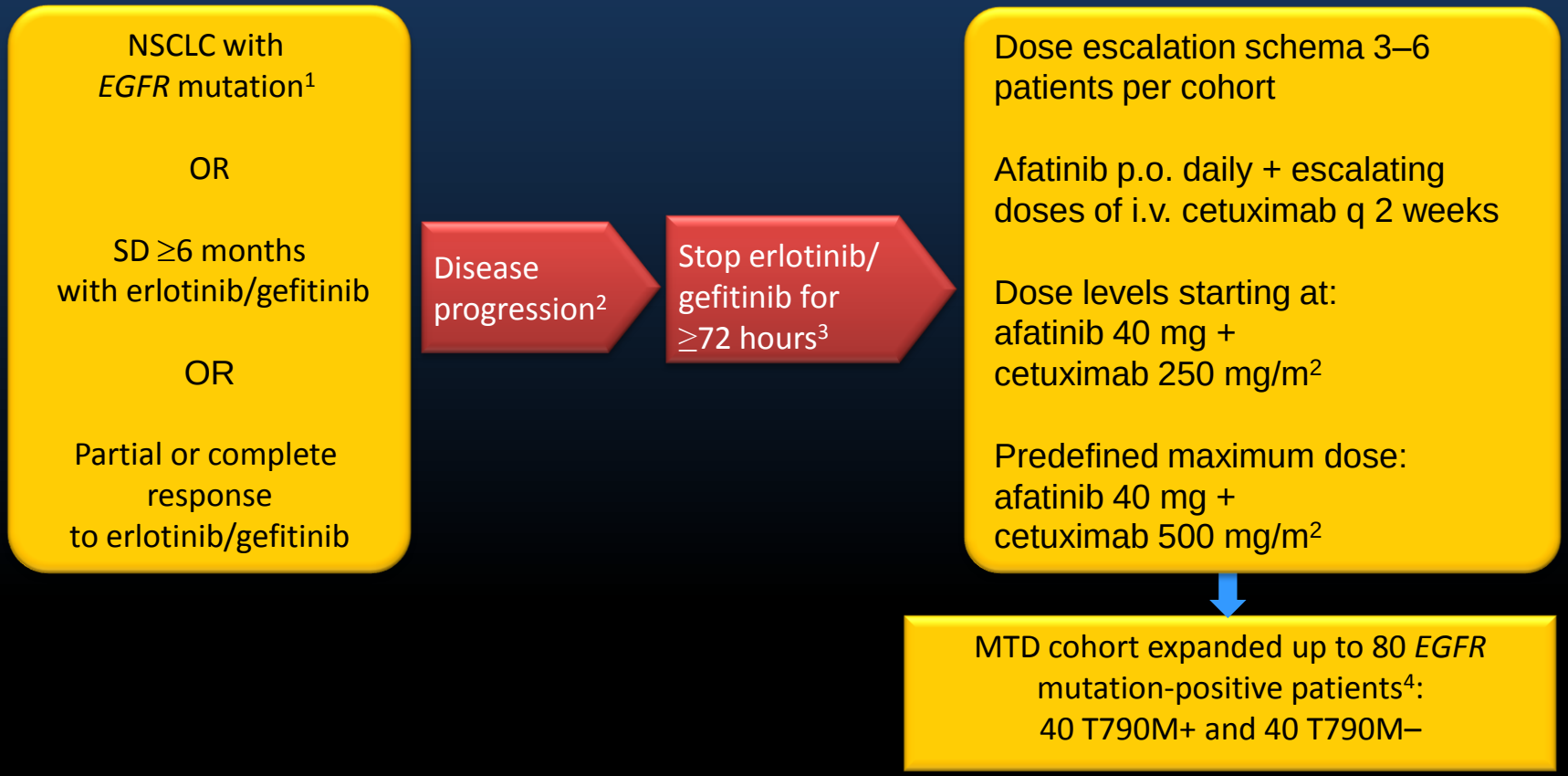
Secondary Outcome Measures:

- Safety of BIBW 2992 when administered together with cetuximab as indicated by intensity and incidence of adverse events, graded according to NCI CTCAE Version 3
  [Time Frame: from day 1 treatment until first documented progression or undue toxicity]
  [Designated as safety issue: Yes]

●この国際臨床試験に日本がどう参加するか？
●耐性に苦しむ患者のために早急に日本で臨床試験、薬剤承認等が必要。
●学問と共に、政治感覚も必要。

Study Design

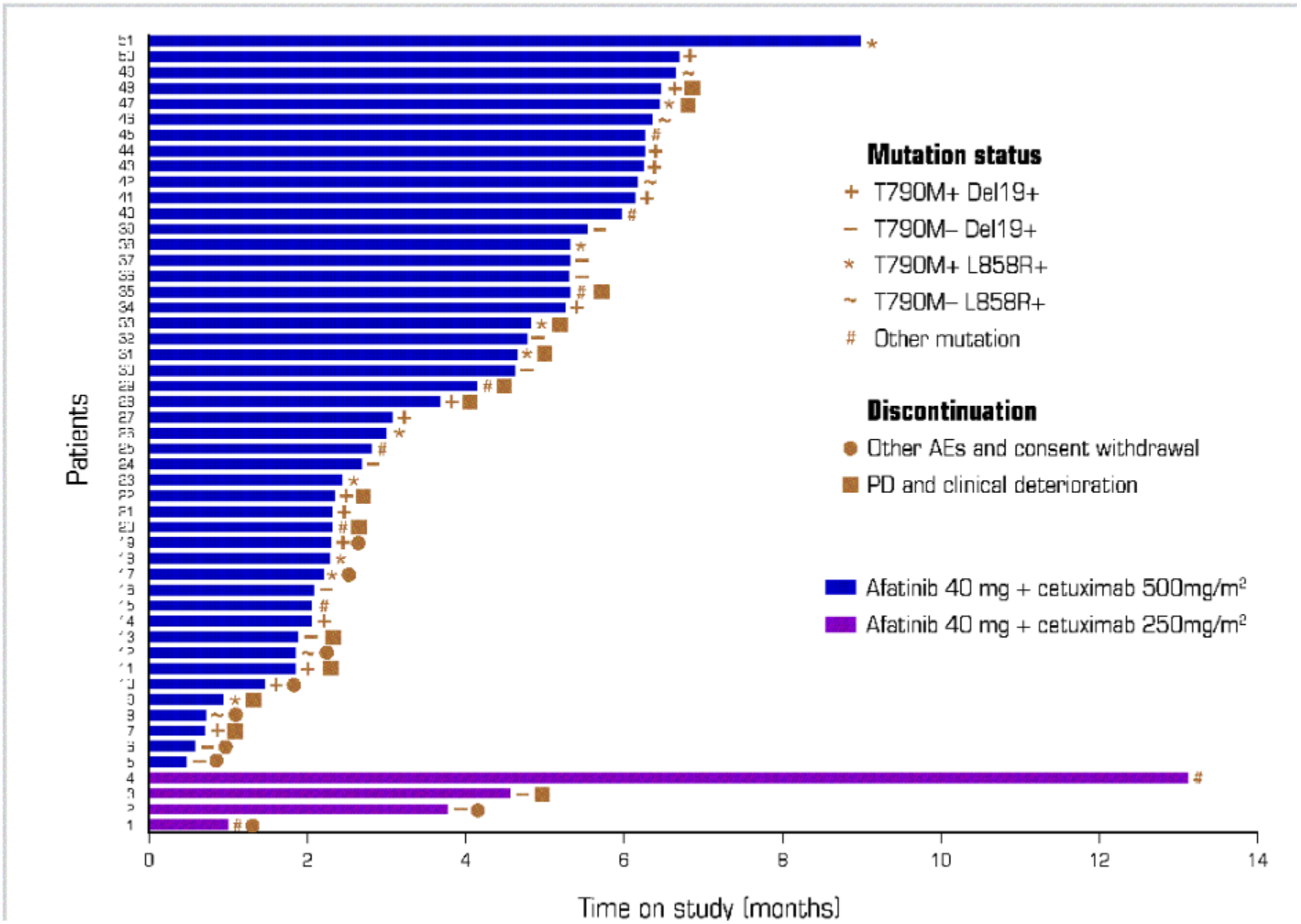
Phase Ib, open-label, multicenter trial in the US and The Netherlands



[1]EGFR G719X, exon 19 deletion, L858R, L861Q; [2]Progression of disease (Response Evaluation Criteria in Solid Tumors v1.1) on continuous treatment with erlotinib or gefitinib within the last 30 days; [3]Amended from original 14-day interval; [4]Acquisition of tumor tissue after the emergence of acquired resistance was mandated.

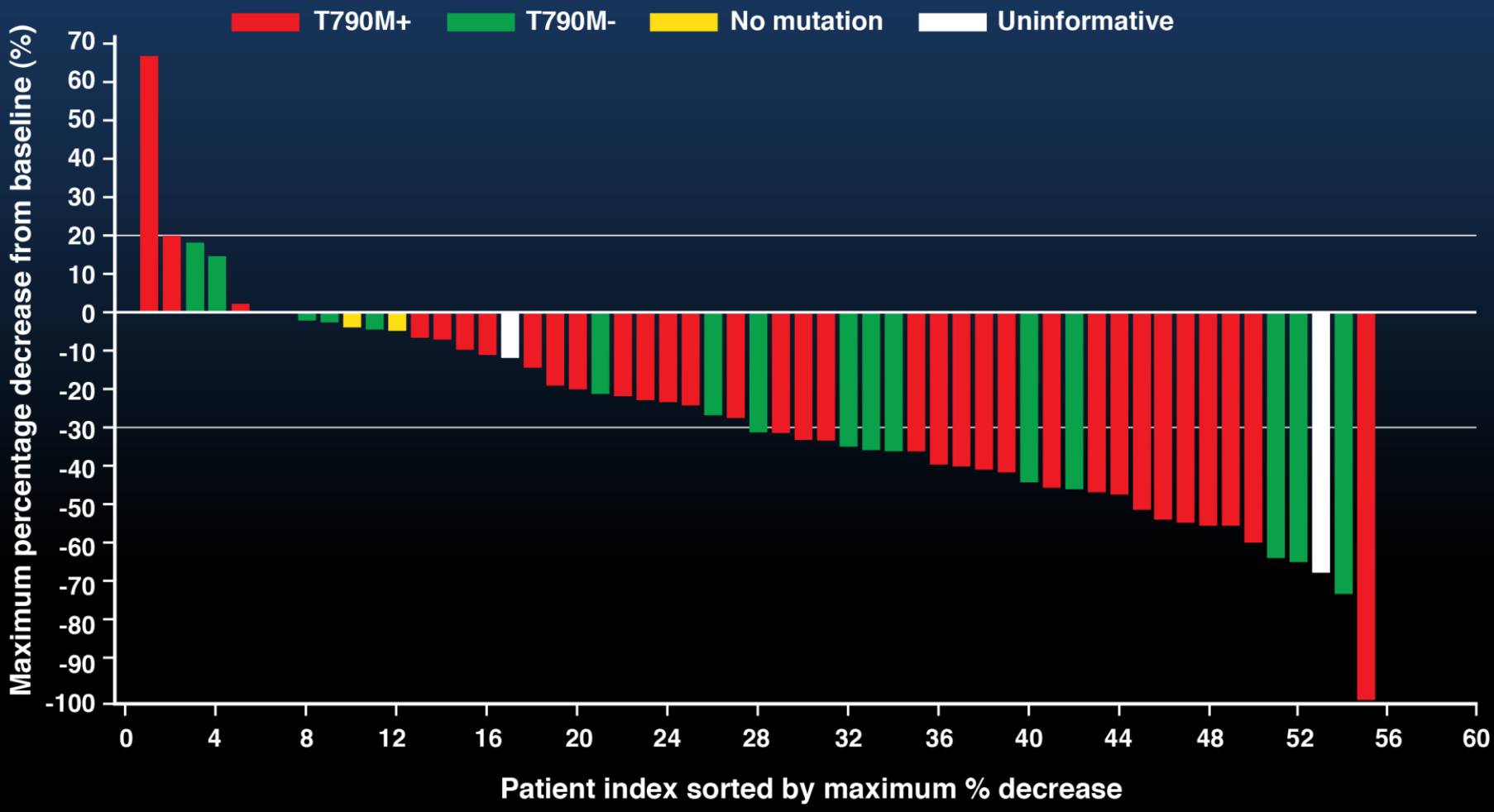
i.v.=intravenous; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; SD=stable disease.

Figure 2: Afatinib + cetuximab exposure



Tumor Regression by T790M Mutation Status

at Recommended Dose



N Engl J Med. 2008 Jul 24.

Detection of Mutations in EGFR in Circulating Lung-Cancer Cells

Maheswaran S, Sequist LV, Nagrath S, Ulkus L, Brannigan B, Collura CV, Inserra E, Diederichs S, Iafrate AJ, Bell DW, Digumarthy S, Muzikansky A, Irimia D, Settleman J, Tompkins RG, Lynch TJ, Toner M, Haber DA.

Table 1. Detection of Circulating Tumor Cells in Patients with Non–Small-Cell Lung Cancer.*

Patient No. and *EGFR* Mutation Status	Sex	Age	Histologic Features	Time since Diagnosis	Previous Systemic Therapy†	Tumor Burden‡	Circulating Tumor Cells§
		yr		*mo*		*cm*	*no. per ml*
EGFR mutation present							
1	M	58	Adeno	3.2	None	19.8	156
2	M	55	Adeno	14.4	C, E	2.4	50
3	F	66	Adeno	18.2	G, C	19.5	9
4	M	59	Adeno/BAC	20.7	G	2.0	771
5	M	57	Adeno	10.8	C	1.5	152
6	F	74	Adeno	18.3	E	9.8	5
7	M	64	NSCLC	13.1	G, E, C	4.6	196
8	F	70	Adeno	1.4	None		
9	F	63	Adeno	0.9	None		
10	F	66	Adeno/BAC	1.3	None	8.2	112
11	F	74	Adeno/BAC	4.8	G	4.5	74
				56.8	G, E, O	7.2	9
				9.9	G	4.1	47
				11	G	5.2	241
				54.7	G, C	30.2	31
				9.2	E	7.0	49
				97.0	G	4.3	103
				29.4	G	13.1	70
				3.0	None	8.8	20
				40.7	G, E, C	7.3	64
				19.7	C, E	2.1	107
				6.4	E	1.4	62
				5.0	E	3.8	62
				1.1	None	22.1	538
				4.6	C	6.7	219
				0.1	None	26.6	84
				15.4	C, E	3.6	43

従来の100倍

ma with bronchoalveolar features, C chemotherapy, E erlotinib, G gefitinib, and O other or experimental agent.
e administered.
ter, according to the Response Evaluation Criteria in Solid Tumors (RECIST).
lated on the basis of the analysis of 1 to 5 ml of whole blood per patient. Patients mple was processed once through the CTC-chip. There was no correlation be- or cells (Spearman's correlation coefficient, −0.02; P=0.88).

Supplementary Table1: Longitudinal analysis of activating *EGFR* genotypes in circulating tumor cells from patients with non small cell lung cancer

Patient Number	1	2	3	10	20	22	23
Mutation at Diagnosis[1]	Del	Del[2]	G719X	L858R	S885L[3]	Del	Del
Time of CTC analysis[4]							
<100d		Del			Del	Del G719X	Del L858R
101-150d	Del			L858R Del			
151-200d	Del			G719X			
201-250d	Del L858R						
251-300d		Del	G719X Del	Del			
301-350d		Del, L858R L861Q	G719X Del				
351-400d		Del		Del			

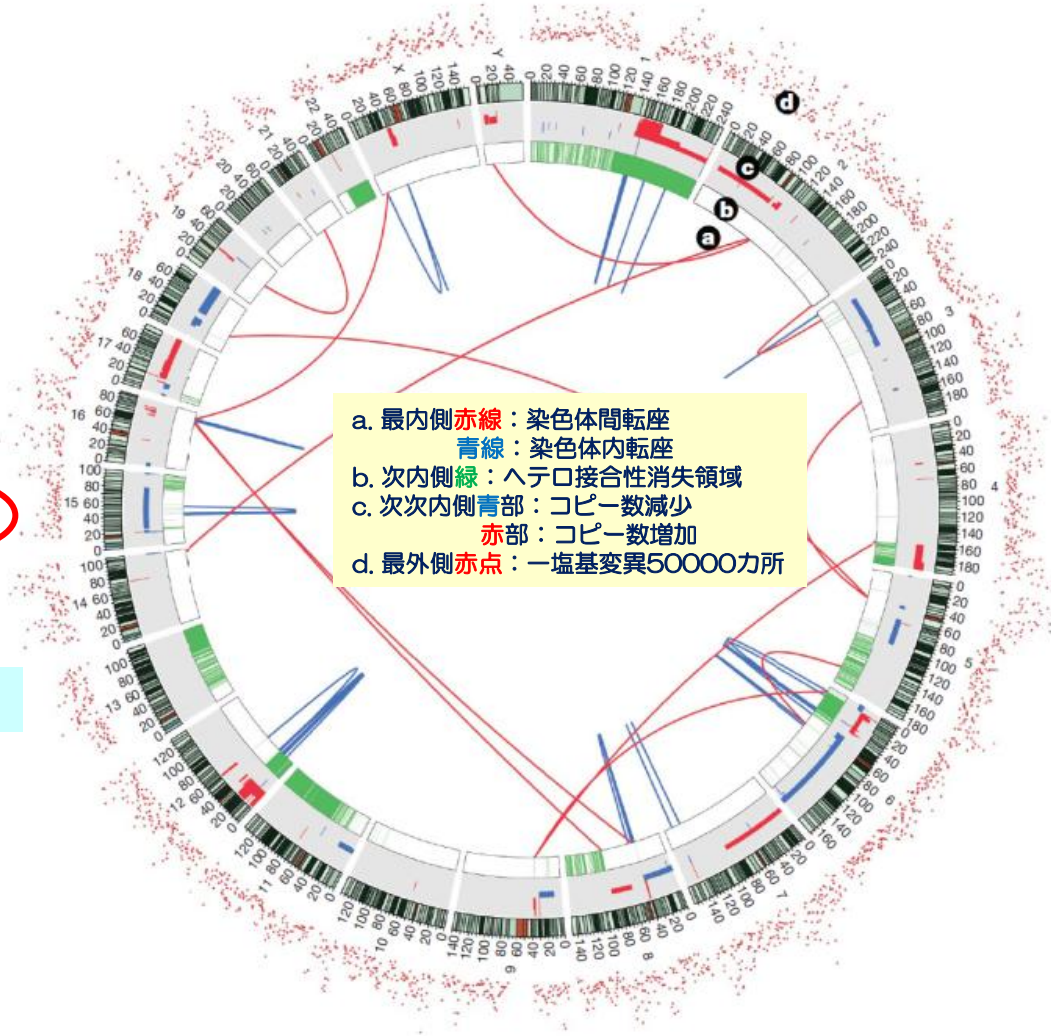
[1]The EGFR mutation at diagnosis was identified by nucleotide sequencing of tumor biopsies at the time of presentation. Serial CTC genotypes, treatment course, CTC quantification and tumor volume measurements for cases 1 and 10 are depicted graphically in figure 2A. Direct *EGFR* nucleotide sequencing of case 2 is shown in Figure 3: [2]The specific deletion mutation identified in the primary tumor differs from that observed in followup CTC specimens. [3]The S885L mutation identified in the tumor specimen is of unknown significance and is not represented in the SARMS assay. No deletion mutation was identified in the tumor. [4]The timing of repeated CTC genotyping analysis following the initial sample is shown in days (d).

肺がんゲノムの全貌：全ゲノム解析の

Nature. 2010 May 27;465(7297):473-7
The mutation spectrum revealed by paired genome sequences from a lung cancer patient.

全ゲノムを２０００ドル以下で解読する技術

Year	reference	Technology	Sample	Average Reported Coverage depth (fold)	Reported sequencing consumables cost	Estimated cost per 40-fold coverage
2007	*S4*	Sanger (ABI)	JCV	7	$10,000,000	$57,000,000
2008	*S5*	Roche(454)	JDW	7	$1,000,000	$5,700,000
2008	*S6*	Illumina	NA18507	30	$250,000	$330,000
2009	*S7*	Helicos	SRQ	28	$48,000	$69,000
2009	this work	this work	NA07022	87	$8,005	$3,700
2009	this work	this work	NA19240	63	$3,451	$2,200
2009	this work	this work	NA20431	45	$1,726	$1,500



全ゲノム情報は予想を凌駕する複雑異常

●確度の高い一塩基変異
50000カ所以上
●体細胞変異
530カ所
●大規模構造改変
43カ所

本論文のsupplで示されたcopy数増減の解析図にとんでもない情報が入っている

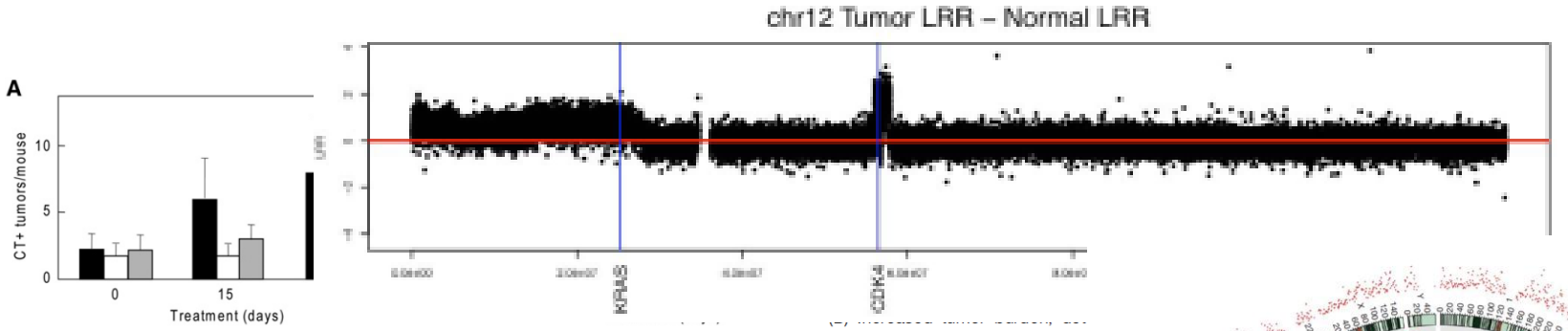
肺がん特異なcdk4阻害：ゲノム解析に答えはあった

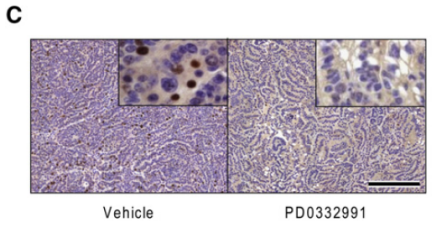
Cancer Cell. 2010 Jul 13;18(1):63-73.

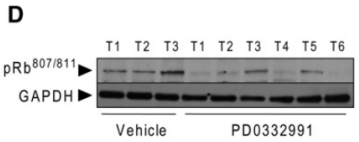
A synthetic lethal interaction between K-Ras oncogenes and Cdk4 unveils a therapeutic strategy for non-small cell lung carcinoma.

Puyol M, Martín A, Dubus P, Mulero F, Pizcueta P, Khan G, Guerra C, Santamaría D, Barbacid M.

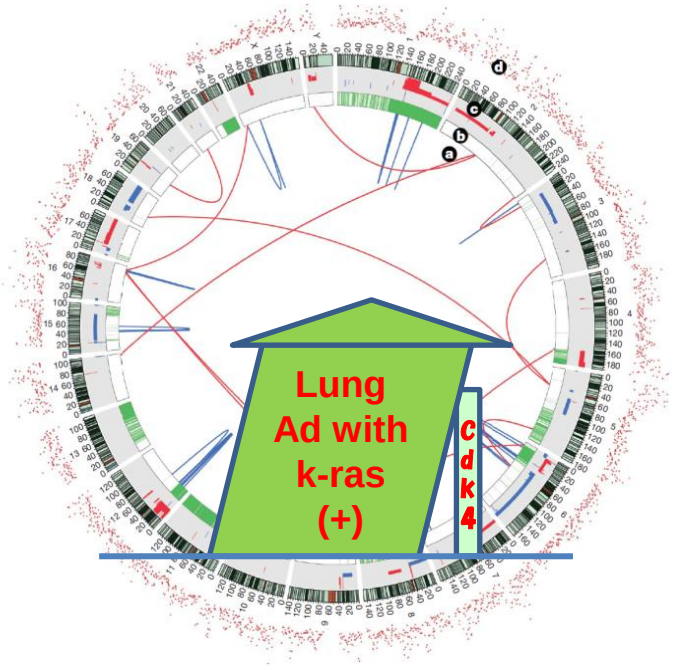
新たな肺癌特異な変化：
Cdk4阻害が増殖抑制を示す
Cdk2、Cdk6は効果なし







analysis, during a 30 day perio
old tumor-bearing K-*Ras*$^{lox/LSLG12}$
Cdk4$^{+/+}$ mice treated as indicate
tumor burden at the beginning of
was 9.68 mm^3, 5.35 mm^3, and
mice treated with either vehicle
7), 100 mg/kg (open bars; n = 6),
(gray bars; n = 6) of PD033299
Data shown represent mean ± SD
(C) Immunohistochemical analysis
lated pRb at Cdk4-specific res
811 in lung sections of K-*R*
RERT$^{ert/ert}$;*Cdk4*$^{+/+}$ mice 1 month after treatment with vehicle (left) or 150 mg/kg of PD0332991 (right). Scale bar: 200 μm. Insert shows a 10
of a representative area.
(D) Western blot analysis of individual tumors microdissected from lungs of K-*Ras*$^{lox/LSLG12Vgeo}$;*RERT*$^{ert/ert}$;*Cdk4*$^{+/+}$ mice 1 month after treatn
vehicle (T1–T3) or 150 mg/kg of PD0332991 (T1–T6) with antibodies specific for pRb phosphorylated at residues Ser807/811. Antibodies
were used as loading controls. Migration of the corresponding proteins is indicated by arrowheads.



Cancer Cell
Article

c-Raf, but Not B-Raf, Is Essential for Development of *K-Ras* Oncogene-Driven Non-Small Cell Lung Carcinoma

Rafael B. Blasco,[1,6] Sarah Francoz,[1,6] David Santamaria,[1] Marta Cañamero,[2] Pierre Dubus,[3] Jean Charron,[4] Manuela Baccarini,[5] and Mariano Barbacid[1,*]
[1]Molecular Oncology
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Centro Nacional de Investigaciones Oncológicas (CNIO), E-28029 Madrid, Spain
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[4]Centre de Recherche en Cancérologie de l'Université Laval, CRCHUQ, Hôtel-Dieu de Québec, Québec, QC G1R 2J6, Canada
[5]Max F. Perutz Laboratories, Center for Molecular Biology, University of Vienna, Vienna 1030, Austria
[6]These authors contributed equally to this work
*Correspondence: mbarbacid@cnio.es

SUMMARY

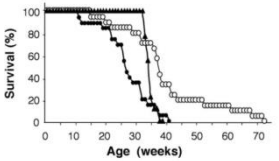
We have investigated the role of individual members of the Raf/Mek/Erk cascade in the onset of K-Ras oncogene-driven non-small cell lung carcinoma (NSCLC). Ablation of Erk1 or Erk2 in K-Ras oncogene-expressing lung cells had no significant effect due to compensatory activities. Yet, elimination of both Erk kinases completely blocked tumor development. Similar results were obtained with Mek kinases. Ablation of B-Raf had no significant effect on tumor development. However, c-Raf expression was absolutely essential for the onset of NSCLC. Interestingly, concomitant elimination of c-Raf and B-Raf in adult mice had no deleterious consequences for normal homeostasis. These results indicate that c-Raf plays a unique role in mediating K-Ras signaling and makes it a suitable target for therapeutic intervention.

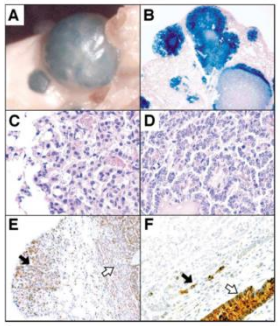
ARTICLE

Tumor induction by an endogenous *K-ras* oncogene is highly dependent on cellular context

Carmen Guerra,[1] Nieves Mijimolle,[1] Alma Dhawahir,[1] Pierre Dubus,[2] Marta Barradas,[3,4] Manuel Serrano,[3,4] Victoria Campuzano,[1] and Mariano Barbacid[1,*]
[1]Molecular Oncology Programme, Centro Nacional de Investigaciones Oncológicas (CNIO), Melchor Fernández Almagro 3, 28029 Madrid, Spain
[2]E.A. 2406, Histologie et Pathologie Moléculaire, Université de Bordeaux 2, 33076 Bordeaux, France
[3]Departamento de Inmunología y Oncología, Centro Nacional de Biotecnología, CSIC, Campus de Cantoblanco, 28049 Madrid, Spain
[4]Present Address: Molecular Oncology Programme, Centro Nacional de Investigaciones Oncológicas (CNIO), 28029 Madrid, Spain
*Correspondence: mbarbacid@cnio.es

Strains of mice	*K-ras* allele§	Proteins expressed ¶
K-ras$^{+/+}$ *K-ras*$^{+/+}$;*CMV-Cre*$^{+/T}$ *K-ras*$^{+/+}$;*RERTn*$^{+/ERT}$	0 → T (35 Kb) 4B pA	K-Ras G12
K-ras$^{+/V12}$ *K-ras*$^{+/V12}$;*RERTn*$^{+/ERT}$	V12 0 Hyg STOP T (35 Kb) 4B IRESgeo pA	None
K-ras$^{+/V12}$;*CMV-Cre*$^{+/T}$ *K-ras*$^{+/V12}$;*RERTn*$^{+/ERT}$ +4OHT	V12 0 T (35 Kb) 4B IRESgeo pA	K-Ras V12 + β-geo





●⑤B-Rafは肺腺癌形成に無関与. ⑥C-RafKOでは肺癌数減少. ⑦全身臓器には無影響、⑧細胞株ではshRNAで増殖抑制.

⑤

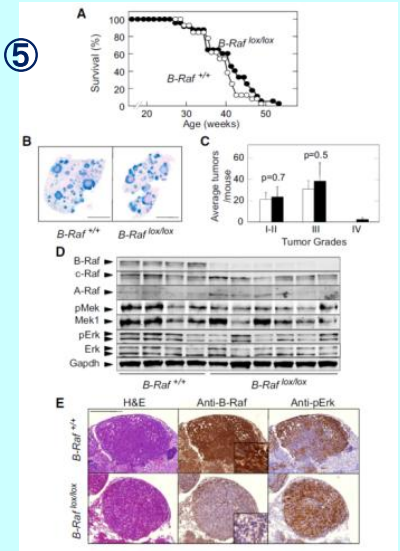
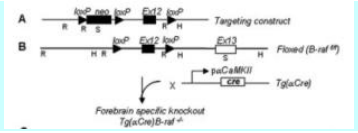
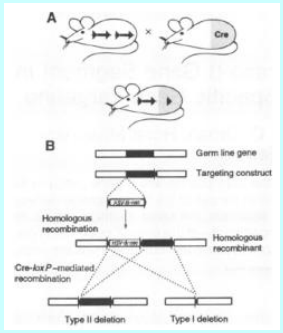


Figure 5. B-Raf Is Not Required for *K-Ras*$^{+/G12V}$-Induced NSCLCs in Mice





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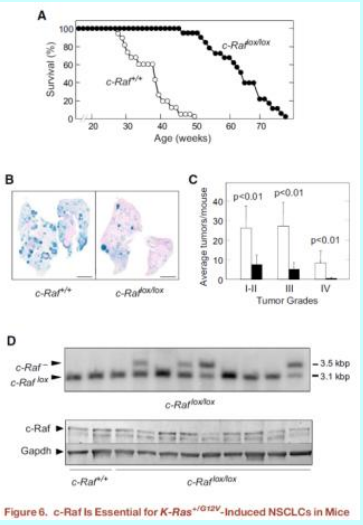
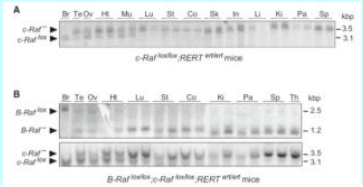


Figure 6. c-Raf Is Essential for *K-Ras*$^{+/G12V}$-Induced NSCLCs in Mice

⑦



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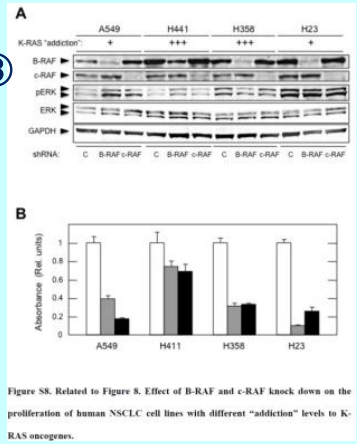
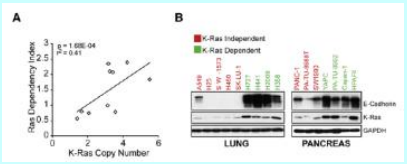
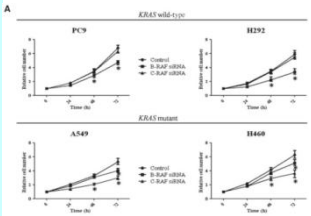


Figure S8. Related to Figure 8. Effect of B-RAF and c-RAF knock down on the proliferation of human NSCLC cell lines with different "addiction" levels to K-RAS oncogenes.





Cancer Res 09: Takezawa, Nakagawa

KEYSTONE SYMPOSIA
on Molecular and Cellular Biology
Accelerating Life Science Discovery

Changing Landscape of the Cancer Genome (F3)

Sponsored by Bayer USA Foundation, Novartis Institutes for BioMedical Research, Onyx Pharmaceuticals, Inc., and Pfizer Inc.

Organizers: Lynda Chin, Christoph Lengauer and Michael Stratton

June 20 - 25, 2011 • Boston Park Plaza & Towers • Boston, Massachusetts

LANGUAGE NOTE: This meeting will be conducted in English.

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Meeting Program

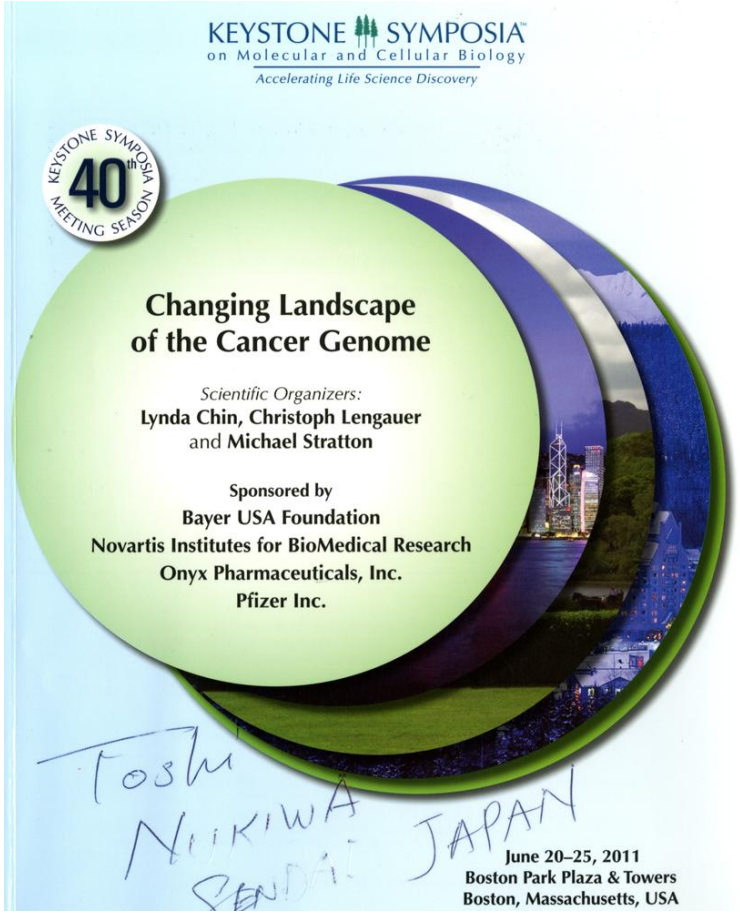
To view program in "24 hour" time (international) click here.

Monday, June 20

3:00 - 7:30 PM	**Registration**	**Imperial Check Room**
6:15 - 7:15 PM	**Refreshments**	**Plaza Ballroom**
7:15 - 8:30 PM	**Welcome and Keynote Address** Registered attendees for this meeting can view Abstracts for this session starting on 05/20/2011 **Thomas J. Hudson,** Ontario Institute for Cancer Research, Canada *Large-Scale Cancer Genomics*	**Imperial Ballroom**

Tuesday, June 21

7:30 - 8:30 AM	**Breakfast**	**Plaza Ballroom**
7:30 - 8:30 AM	**Poster Setup**	**Plaza Ballroom**
8:30 AM- 5:00 PM	**Poster Viewing**	**Plaza Ballroom**
8:30 AM- 12:00 PM	**Integrative Cancer Genome Projects** Registered attendees for this meeting can view Abstracts for this session starting on 05/20/2011 **Lynda Chin,** Dana-Farber Cancer Institute, TCGA, USA *The Genomic Landscape of Glioblastoma* **Nabahet Ameur,** Memorial Sloan Kettering Cancer Center, USA *Short Talk: Integrated Genomic Analysis and Next Generation Sequencing of Rhabdomyosarcoma Reveals Novel Molecular*	**Imperial Ballroom**

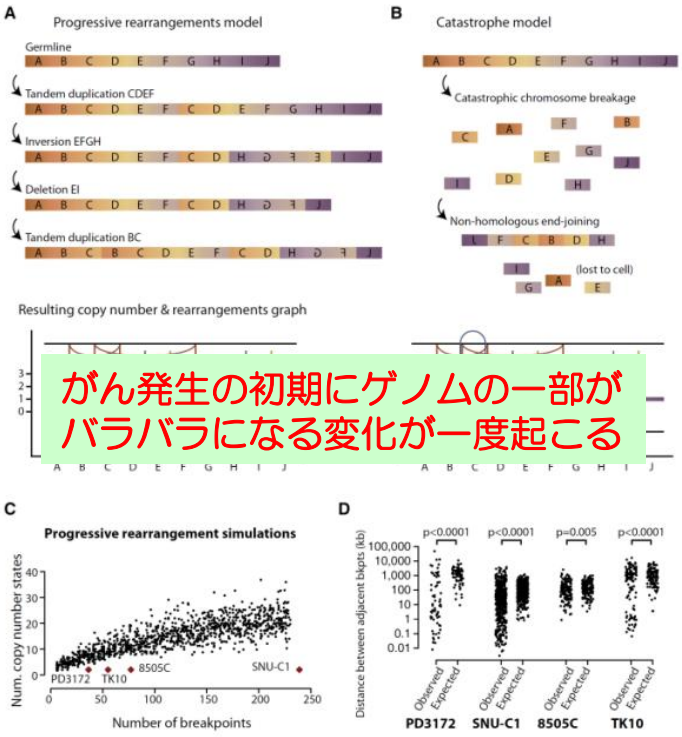


Chromothripsis：新たな癌ゲノム理念

Chromothripsis
（chromosome+shattered into pieces）

Massive Genomic Rearrangement Acquired in a Single Catastrophic Event during Cancer Development

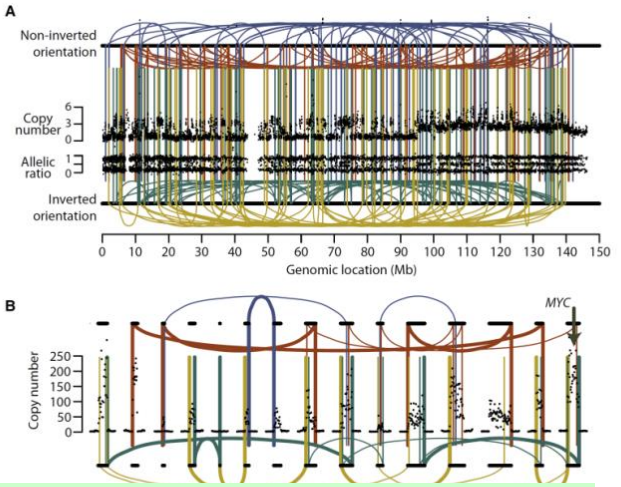
Cell, 144, 27, 2011



がん発生の初期にゲノムの一部がバラバラになる変化が一度起こる

Figure 5. Genomic Features of Chromothripsis Suggest that Most Rearrangements Occur in a Single Catastrophic Event
(A) Example of a sequence of progressive rearrangements disrupting a model chromosome. The chromosomal configuration after each rearrangement is shown, together with the copy number and rearrangement plot that would result (in the style of Figure 2).
(B) Example of how a chromosomal catastrophe might break the chromosome into many pieces that are then stitched back together haphazardly.
(C) One thousand Monte Carlo simulations (black points) performed under the assumption that rearrangements accumulate progressively over time show the number of copy number states seen in the resultant derivative chromosome. Samples with chromothripsis, shown as red diamonds, fall well outside this spectrum.
(D) Observed distances between adjacent breakpoints for each sample are shown beside the expected distribution if breaks occurred in entirely random locations.

Double minute chromosome（ミニ染色体）
もともと薬剤耐性で70年代より知られていた



がんゲノムの一部は、ミニ染色体となり、コピー数が数10倍になる

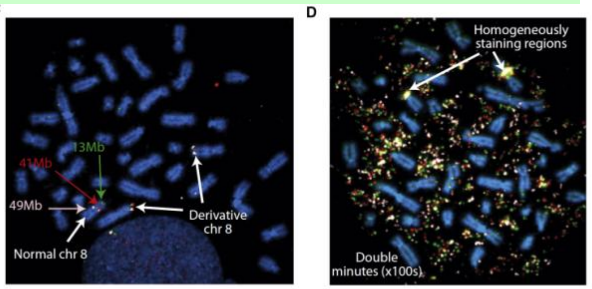


Figure 6. Generation of a Double Minute Chromosome Containing *MYC* by Chromothripsis in a Small Cell Lung Cancer Cell Line, SCLC-21H
(A) Copy number profile, allelic ratio, and rearrangements of chromosome 8.
(B) Copy number data from the rearrangement screen shows 15 discrete regions of chromosome 8 that are massively amplified, with 50–200 copies per cell. Each amplified region is demarcated by rearrangements linking to other heavily amplified segments (thick lines), with evidence for later internal rearrangements also found (thin lines).
(C) Three color FISH for three regions of chromosome 8 (predicted to be linked by the rearrangement data, but not amplified; green, 13 Mb; red, 41 Mb; pale pink, 49 Mb).
(D) FISH for three heavily amplified regions. The locations of the probes are shown in Figure 6B (red, 66.5 Mb; white, 99.3 Mb; green, 128.8 Mb).

Anti-cancer Immunotherapy：ようやく実効の時代？

- MDX 1106 (BMS 936558/ONO 4538)
  - A fully human anti PD-1 IgG4
  - High affinity binding to human and cynomolgus PD-1
  - Blocks binding of PD-1 to PD-L1 and PD-L2
  - *In vitro*, promotes cytokine production/proliferation
    - human allogeneic mixed lymphocyte reaction (MLR)
    - Ag reactive T cells in response to CMV or tumor Ag
  - reverses T_{reg} mediated suppression of allogeneic MLR

ClinicalTrials.gov
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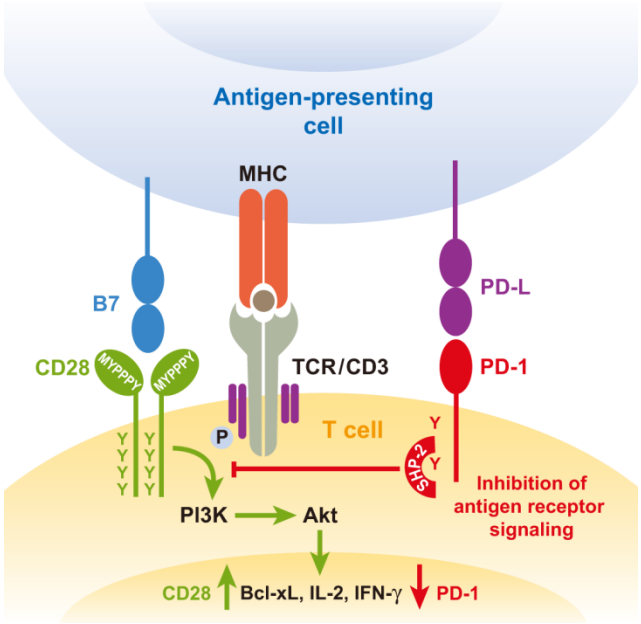
A Phase 1b Study of MDX-1106 in Subjects With Advanced or Recurrent Malignancies (MDX1106-03)

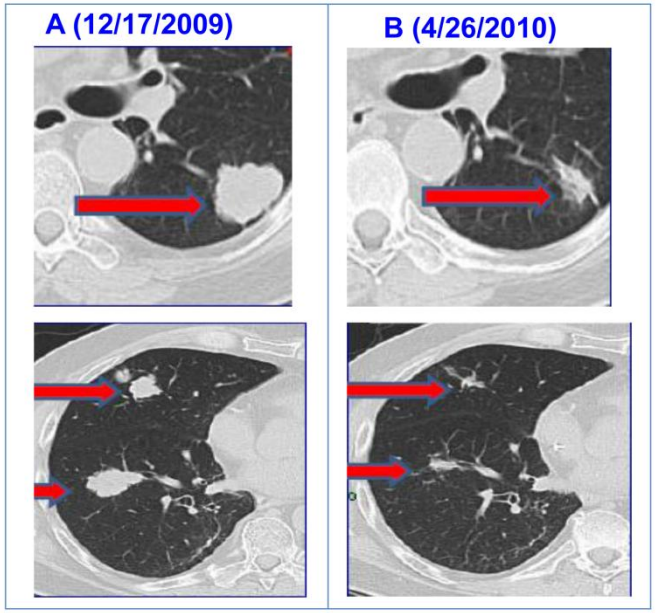
This study is currently recruiting participants.
Verified on July 2011 by Bristol-Myers Squibb

First Received on August 4, 2008. Last Updated on July 27, 2011 History of Changes

Sponsor:	Bristol-Myers Squibb
Collaborator:	Ono Pharmaceutical Company, Ltd.
Information provided by:	Bristol-Myers Squibb
ClinicalTrials.gov Identifier:	NCT00730639



ACTIVITY IN NSCLC: 10 MG/KG



60 yr/male patient

•diagnosed in 2002

•Intermittent responses but eventual progression on multiple prior combination chemotherapies and radiation therapy

A: Baseline

B: Cycle 2 assessment

J. Brahmer, Johns Hopkins University

cancer immunotherapy trials network

最近20年の猛烈な遺伝子研究技術革新

21世紀遺伝子研究技術革新（高集積90万SNPs、評価技術、高速演算）

	Human genome project	High throughput technology	遺伝子・呼吸器内科　貫和
1990	Human genome project by $3 billion; Dep. of Energy and NIH		
1993	Collins, F, (National Human Genome Research Institute: NHGRI) Venter C, (Celera Genomics, 1988)	MALDI-TOFMS (1994)	貫和：東北大学加齢研赴任 ヒトゲノム解読は30年？ ヒト遺伝子数：10万種？
1995	Haemophilus influenzae genome (1995) Saccharomyces cerevisiae genome (1996)	Microarray concept (1995)	研究プロジェクト：遺伝子治療
1998	Caenorhabditis elegans genome (1998)	Affymetrix microarray (1996)	アデノウイルス・ベクター使用による前臨床癌遺伝子治療
	Drosophila melanogaster genome (2000)		
2000	Human genome rough draft (2000)		P53遺伝子治療　第一例(06, 2000) 医学部附属病院へ引っ越し(09, 2000)
2003	HapMap project start (2002) Human genome project complete (2003)　23000 genes	Affymetrix U133 plus 2.0 (2005)	肺癌分子標的薬イレッサ承認(08, 2002) EGFR-TK活性化変異発見 個別化医療推進 初回治療臨床試験
2005	HapMap project phase I (2005) 1000,000 SNPs Copy number variation (2006) $1000/genome project (2006, NHRGRI) HapMap project phase II (2007) 3000,000 SNPs	Pyrosequencing (2005) Illumina Solexa genome analizer (2005) Genome-Wide Human SNP Array 6.0 9 x 105 SNPs with CNV (2007)	医学部異動：呼吸器病態学分野(12, 2007) EGFR driver mutation: Gefitinib first (NEJM, 2010)
2011		DNA nanoarray (2010) SMRT (single molecule real time sequencing 2003, 2010, 2011)	

最近20年の猛烈な遺伝子研究技術革新

21世紀遺伝子研究技術革新（高集積90万SNPs、評価技術、高速演算）

Human genome project

High throughput technology

遺伝子・呼吸器内科　貫和

1990 Human genome project by $3 billion; Dep. of Energy and NIH

1993 Collins, F, (National Human Genome Research Institute: NHGRI)
Venter C, (Celera Genomics, 1988)

1995 Haemophilus influenzae genome (1995)
Saccharomyces cerevisiae genome (1996)

1998 Caenorhabditis elegans genome (1998)

Drosophila melanogaster genome (2000)

がん（象）の全体像が分かる時代

2000 Human genome rough draft (200(

HapMap project start (2002)

2003 **Human genome project complete (2003) 23000 genes**

HapMap project phase I (2005)
1000,000 SNPs

2005 Copy number variation (2006)
$1000/genome project (2006, NHRGRI)

HapMap project phase II (2007)
3000,000 SNPs

2011

Pyrosequencing (2005)
Illumina Solexa genome analizer (2005)

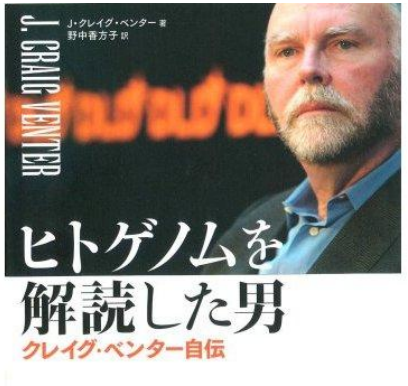
Genome-Wide Human SNP Array 6.0
9 x 105 SNPs with CNV (2007)

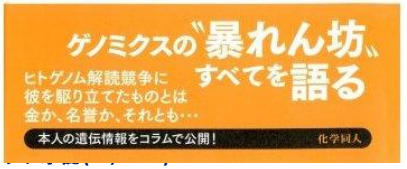
DNA nanoarray (2010)
SMRT (single molecule real time sequencing
2003, 2010, 2011)

貫和：東北大
ヒトゲノム解
ヒト遺伝子

研究プロジ

アデノウイル
伝子治療





肺癌分子標

EGFR-TK活性化変異発見
個別化医療推進
初回治療臨床試験

医学部異動：呼吸器病態学分野(12, 2007)

EGFR driver mutation: Gefitinib first (NEJM, 2010)

現代基礎研究は臨床に直結している―21世紀医療はゲノム理解が重要！